

# *In the Supreme Court of the United States*

OCTOBER TERM, 1972

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No. 72-394

ELLIOT L. RICHARDSON, ET AL., PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

*ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS  
FOR THE FOURTH CIRCUIT*

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No. 72-414

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL.

*ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS  
FOR THE FOURTH CIRCUIT*

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No. 72-528

CIBA CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL.

*ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS  
FOR THE THIRD CIRCUIT*

---

No. 72-555

ELLIOT L. RICHARDSON, ET AL., PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

*ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS  
FOR THE FOURTH CIRCUIT*

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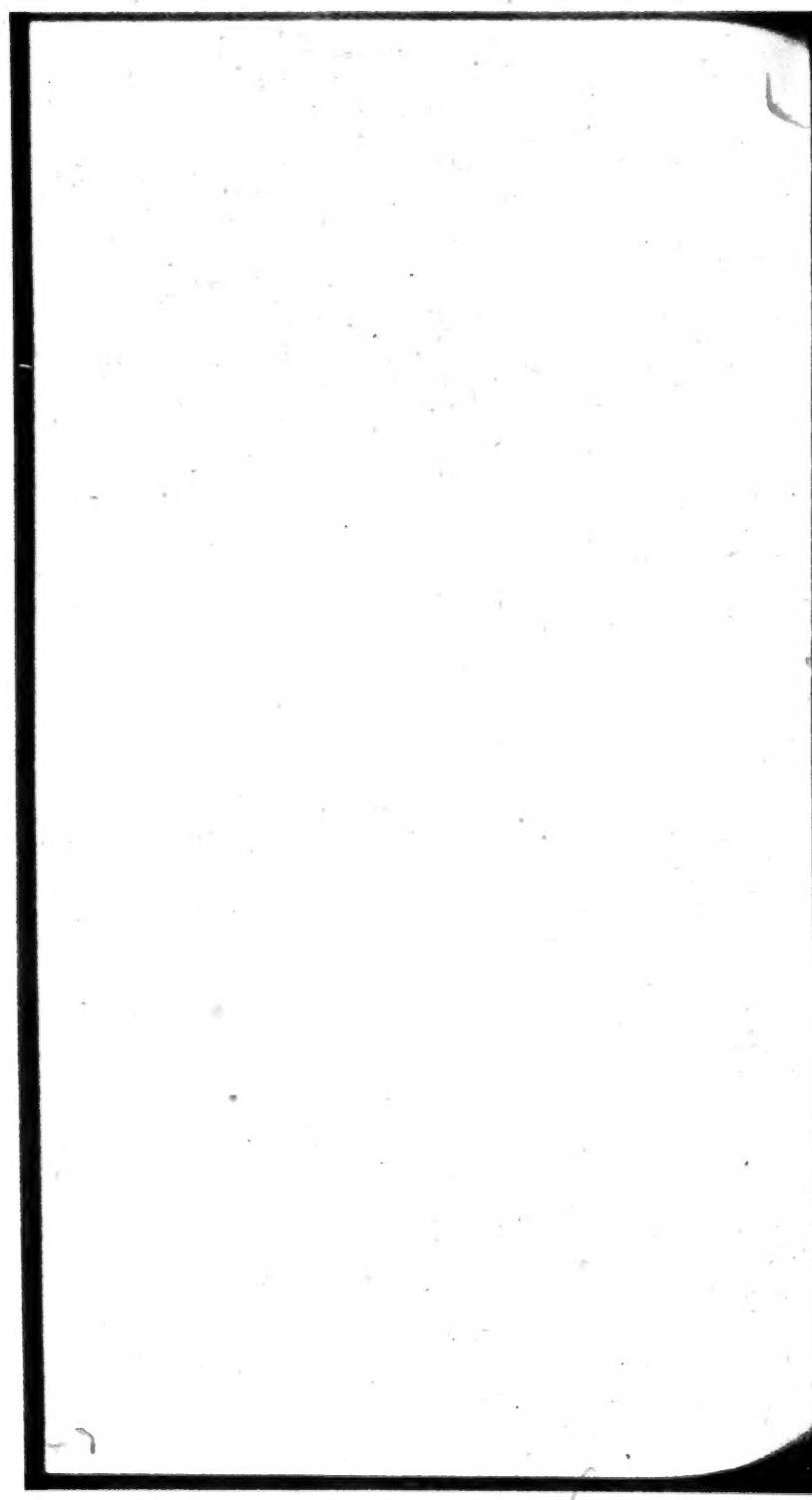
No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

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*ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS  
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## CIBA CORPORATION, PETITIONER

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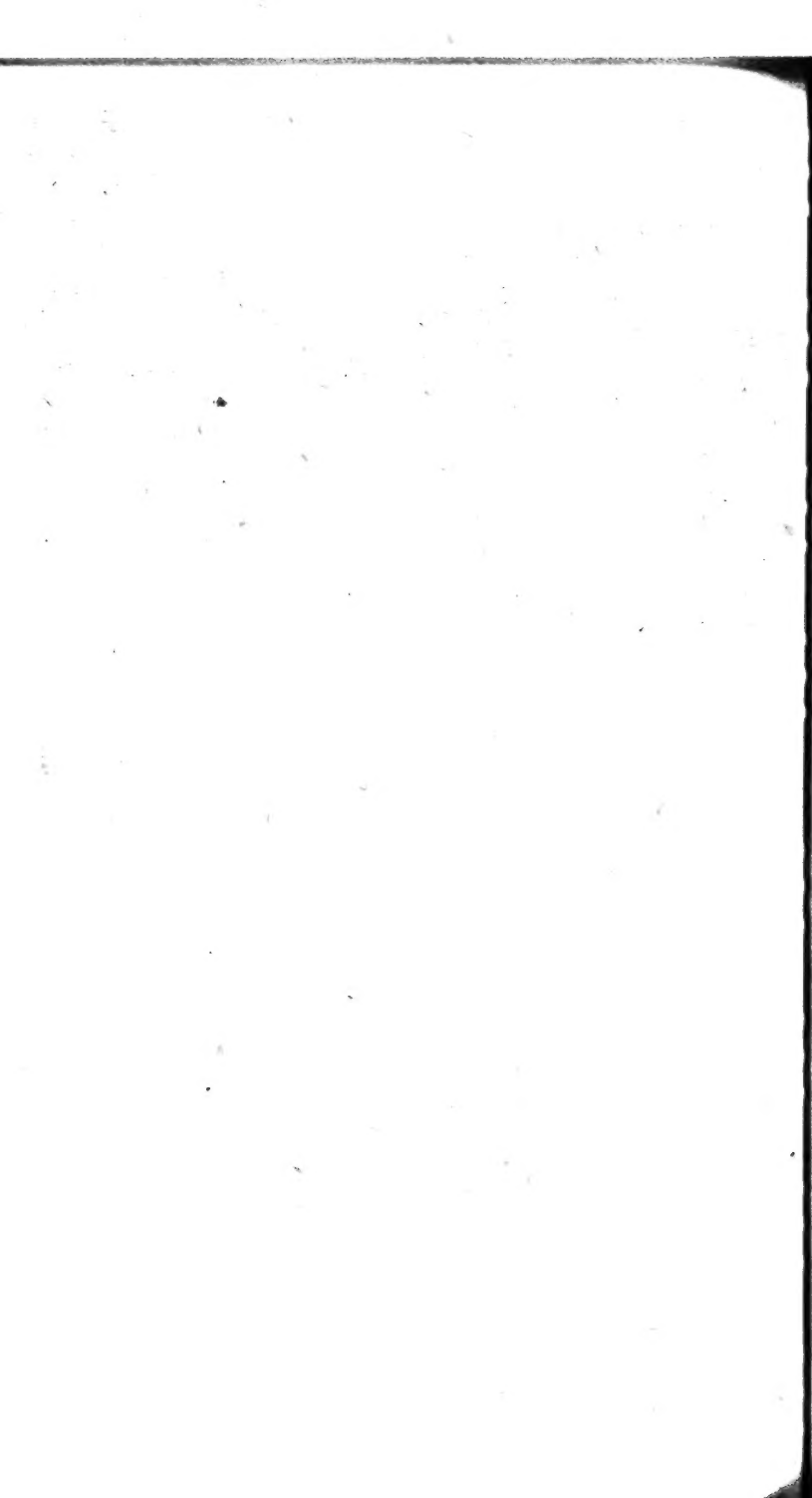
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## RELEVANT STATUTES AND REGULATIONS

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In the United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL., RESPONDENTS

RELEVANT DOCKET ENTRIES

Date

- 7/30/71 Petition to set aside order of Commissioner of Food and Drugs filed and cause docketed.
- 7/30/71 Notification of the filing of the petition, together with a copy of the petition, transmitted to the respondents in Washington, D.C.
- 8/ 4/71 Appearances (2) for the petitioner filed and entered.
- 8/ 6/71 Appearance for the petitioner filed and entered.
- 9/13/71 Certified list of record filed.
- 10/ 4/71 Appearances (2) for the respondents filed and entered.
- 10/26/71 Brief for petitioner filed. 25 copies.
- 10/26/71 Joint appendix filed. 10 copies of volume I and II.
- 11/19/71 Respondents' request for an extension of time to file their brief filed.
- 11/19/71 Order extending time to file respondents' brief to December 2, 1971, filed.
- 12/15/71 Brief for respondent filed. 25 copies.
- 12/21/71 Reply brief for petitioner filed. 25 copies.
- 1/13/72 Motion of USV Pharmaceutical Corp. for leave to present oral argument as amicus curiae, filed.
- 1/14/72 Notice of oral argument mailed to Edward, Williams, Williams, Worley, Patterson, Epstein,

McConachie, Hovendon, McLaren, Hutt, and Pfeifer.

- 1/19/72 Order granting USV Pharmaceutical Corp. leave to present oral argument as amicus curiae, filed.
- 1/24/72 Opposition to motion of USV Pharmaceutical Corp. for leave to present oral argument as amicus curiae, filed.
- 1/24/72 Appearance for amicus curiae filed and entered.
- 1/25/72 Memorandum for USV Pharmaceutical Corp. in opposition on respondent's motion for reconsideration of order granting leave to argue as amicus curiae, filed.
- 1/31/72 Order denying government's motion to reconsider, filed.
- 2/ 2/72 Brief (or memorandum) for amicus curiae filed. 25 copies.
- 2/ 3/72 Respondent's petition for oral argument to memorandum and argument of amicus curiae, filed.
- 2/ 7/72 Appearance for the respondents filed and entered.
- 2/ 7/72 Cause argued before Butzner, Russell and Field, Circuit Judges, and submitted.
- 2/18/72 Tape mailed to Judge Russell.
- 5/24/72 Opinion filed.
- 5/24/72 Opinion and Clerk's Memorandum mailed to counsel of record. (Mailed to Hoffman, Williams, Williams, Worley, McConachie, Epstein, and Hovendon.)
- 5/24/72 Decree filed. Order of the Commissioner reversed.
- 6/ 5/72 Petitioner's verified bill of costs, filed.
- 6/15/72 Certified copy of the decree and printed copy of the opinion transmitted to the Commissioner of Food and Drugs, Dept. of Health, Education and Welfare.
- 9/13/72 Notice evidencing filing petition for certiorari in the Supreme Court September 11, 1972 filed. (Hynson, Westcott and Dunning, Inc. No. 72-414).



- 9/13/72 Notice evidencing filing petition for writ of certiorari in the Supreme Court September 11, 1972 filed. (Elliot Richardson—No. 72-394).
- 10/ 3/72 Certified copies of Volumes I and II of the joint appendix transmitted to the Clerk of the Supreme Court.
- 1/12/73 Certified copy of order of the Supreme Court granting certiorari January 8, 1973 filed.
- 2/ 2/73 Certified record in one volume transmitted to the Clerk of the Supreme Court.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
*Washington 25, D.C., Dec. 23, 1953.*

NDA 8986

HYNSON, WESTCOTT & DUNNING  
(Attention: Dr. John H. Brewer)  
*Charles and Chase Streets,  
Baltimore, Maryland.*

GENTLEMEN: This will acknowledge your letter of November 4, 1953 and additional information on the manufacturing process personally submitted by Dr. John H. Brewer on November 4, 1953 with reference to your new drug application for "Lutrexin". The application was filed with the Secretary on November 5, 1953.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Act it has become effective.

Our affirmative action in allowing this application to become effective is based on safety alone. All claims are on your own responsibility.

In our opinion the studies submitted with the application were not sufficiently controlled to support the conclusion that "Lutrexin" is an effective treatment for dysmenorrhea, habitual and threatened abortion. We recommend that the article not be marketed for these purposes until adequate evidence is available to demonstrate its value. We believe that it is particularly important not to offer the article at this time for use in habitual and threatened abortion because of the hazards

involved in relying upon a drug the effectiveness of which has not been established.

The label statements "Each tablet contains —— uterine relaxing factor units" may create the misleading impression that this represents a unit of clinical activity. We suggest that it be revised to read "Each tablet contains —— guinea pig uterine relaxing factor units". Further, it is recommended that the brochure include the definition of the unit. It is also recommended that the brochure be packaged with the drug. Unless this is done, it is required that the label bear a statement of the usual or recommended dosage in order to comply with the regulation 1.106(b) under section 502(f) of the Act.

Please submit five copies of the final printed label and labeling when available.

Sincerely yours,

(S) Ernest Q. King, M.D.,  
ERNEST Q. KING, M.D.,  
*Acting Medical Director.*

Enclosure:

Effective paragraphs.

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,

FOOD AND DRUG ADMINISTRATION.

*Washington 25, D.C., Mar. 23, 1956.*

NDA 10144

HYNSON, WESTCOTT AND DUNNING, INC.,

(Attention: Mr. McLaughlin),

*Charles and Chase Streets,*

*Baltimore, Maryland.*

GENTLEMEN: This will acknowledge your communications of January 27 and February 29, 1956 submitting additional pertinent information on controls and copies of revised labels pertaining to your new drug application for the preparation "Trexinest". Also acknowledged are communications of November 1, 1955 and February 16, 1956 from The Burrough Bros. Mfg. Co., Baltimore, Md. setting the methods, facilities, and controls they will employ in coating the tablets for you. In addition this will acknowledge a letter dated February 27, 1956 from International Hormones, Inc., Brooklyn, New York, specifying the type conjugated estrogens they will supply to

you and a letter of February 20, 1956 from the Laboratory of Industrial Hygiene, Inc., New York, New York setting forth the procedure they will employ in assaying the tablets for you. The application was filed on March 1, 1956.

Our only comment with respect to the labeling is to suggest the addition of a paragraph containing all the usual estrogen warnings.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Act it has become effective.

Our affirmative action in allowing this application to become effective is based upon considerations of safety alone. Any claims which you make are upon your own responsibility.

Please submit five copies of the final printed label and labeling and three finished market packages of the drug when available.

Sincerely yours,

(S) Barbara Moulton, M.D.,  
BARBARA MOULTON, M.D.,

*Medical Officer, New Drug Branch, Division of Medicine.*

Enclosure:

Effective paragraph.

*National Academy of Sciences-National Research  
Council*

(Log 1346)

DIVISION OF MEDICAL SCIENCES

DRUG EFFICACY STUDY

*Form A (To be submitted in duplicate by applicant)*

1. NDA Number 8986.
2. Date Originally Approved December 23, 1953.
3. Rx ☐ OTC ☐.
4. Brand Name Lutrexin <sup>®</sup> Tablets.
5. Applicant's Name Hynson, Westcott & Dunning, Inc.  
and Address Charles & Chase Streets, Baltimore,  
Maryland 21201.

6. Quantitative Formula, Established (Non-Proprietary)  
Name of Active Ingredients (in order shown on label) Lutu-  
trin: Amount (per tablet, per ml., etc.) 3000 units per tablet.

7. Dosage Form (tablets, etc.) Tablets.

8. Route of Adm. (Oral, etc. Where a new drug application  
covers different routes of administration, separate forms should  
be used.) Oral.

9. Therapeutic Claims—Attach 10 labels and 10 package  
inserts (if used) to original Form A (blue) and 1 copy to dupli-  
cate Form A (white).

10. List of literature references most pertinent to an evalua-  
tion of the effectiveness of the drug for the purposes for which  
it is offered in the label, the package insert, or brochure. Ap-  
proximately 5 to 10 key references are requested, if available.  
(Attach 10 copies to original Form A (blue) and 1 copy to  
duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any  
unpublished material that is pertinent to the evaluation of the  
drug by the Academy—Research Council. This supplementary  
material should be packaged with Form A (white). A single  
copy of this material is requested. The attached paper by Dr.  
Rizzolo has been accepted for publication by Clinical Medicine.

12. In this space, please list and describe briefly the supple-  
mentary material that is submitted with Form A (white). Our  
files contain hundreds of testimonial letters from physicians  
who have used Lutrexin successfully with their families  
(sample copy attached).

(Blue copy is original—White copy is duplicate—the back  
of this form may be used if additional space is needed)

Lutrexin Tablets  
NDA 8986  
LOG 1346

PANEL ON DRUGS USED IN DISTURBANCES OF THE  
REPRODUCTIVE SYSTEM

INDICATIONS

*I. Functional dysmenorrhea*

EVALUATION: Possibly effective.

COMMENTS: Because the efficacy of remedies for dysmenorrhea is determined principally by a subjective criterion (i.e., report of relief by the patient), it is the opinion of the Panel that firm reliance can be placed only on data obtained from studies that are well controlled. Although the reports cited below suggest that Lutrexin Tablets may produce varying degrees of relief from dysmenorrhea in some patients, it is the opinion of the Panel that only limited credence can be given to these findings because the designs of the experiments were defective in certain respects. Among the defects noted were failure to use the double-blind technique, inadequate duration of the studies, and populations of subjects too small to be meaningful. The efficacy of Lutrexin Tablets for this indication cannot be determined until the results of well-controlled studies are available for evaluation. This indication should be considered inappropriate if sound documentation is not supplied by the manufacturer.

DOCUMENTATION:

1. Hayden, G. E. Relief of primary dysmenorrhea. *Obstet. Gynec.* 16:730, 1960.
2. Jones, S. S. Lututrin: a new drug for relief of dysmenorrhea. *Northwest Med.* 54:1253, 1955.

*II. Selected cases of premature labor*

EVALUATION: Possibly effective.

COMMENTS: This indication poses several difficulties. The package insert stipulates "selected cases." but offers no criteria

on which the selection is to be made. The manufacturer does not define or describe this indication satisfactorily in the package insert; rather, the reader is referred merely to two clinical reports dealing with "premature labor." In these reports, the authors describe instances where, in their opinion, the threat of premature labor existed. They say that, in many of these cases, they were able to prevent the onset of labor by the administration of Lutrexin Tablets. It is the opinion of the Panel that the diagnosis of premature labor can be made only when labor has clearly started and that one cannot predict which patients will go into premature labor. Therefore, the Panel cannot evaluate the efficacy of Lutrexin Tablets in preventing the onset of premature labor, as one cannot know, with a satisfactory degree of certainty, in which patients premature labor will probably develop. The Panel believes, on the basis of the documentation received and their own experience, that this claim is unwarranted.

DOCUMENTATION: None applicable.

### *III. Threatened and habitual abortion*

EVALUATION: Possibly effective.

COMMENTS: The Panel knows of no satisfactory evidence to support this claim. The claim should be considered inappropriate unless efficacy can be proved by additional documentation provided by the manufacturer.

DOCUMENTATION: None available.

Approved by:

(s) ALBERT SEGALOFF, *Chairman.*

### *National Academy of Sciences-National Research Council*

[Received Jan. 28, 1970]

DIVISION OF MEDICAL SCIENCES

DRUG EFFICACY STUDY

*Form A (To be submitted in duplicate by applicant)*

1. NDA Number 10144.
2. Date Originally Approved March 23, 1956.  
Supplement effective March 4, 1959.
3. Rx ☒ OTC ☐

4. Brand Name Trexinest® Tablets.

5. Applicant's Name Hynson, Westcott & Dunning, Inc. and Address Charles & Chase Streets, Baltimore, Maryland 21201.

6. Quantitative Formula, Established (Non-Proprietary) Name of Active Ingredients (in order shown on label) Sodium Estrone Sulfate, Lututrin. Amount (per tablet, per ml., etc.) 1.0 mg. 500 units.

7. Dosage Form (tablets, etc.) Tablets.

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral.

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white). (Blue copy is original—White copy is duplicate—the back of this form may be used if additional space is needed)

TREXINEST

NDA 10144

LOG 825

PANEL ON DRUGS USED IN DISTURBANCES OF THE  
REPRODUCTIVE SYSTEM

INDICATIONS

*I. Menopausal disorders*

EVALUATION: Effective, but \* \* \*.

COMMENTS: The estrogenic component of this preparation is a recognized effective therapy for the menopausal syndrome, but there is no evidence that lututrin adds to the

effectiveness of the combination. This claim should be considered inapplicable unless the company can provide sound documentation that lututrin enhances the effectiveness of estrogen in the menopausal syndrome. The documentation submitted originally was anecdotal.

DOCUMENTATION: Inadequate.

Approved by:

(S) ALBERT SEGALOFF, *Chairman.*

33 F.R. 7701 (May 24, 1968)

## *Food and Drug Administration*

### DRUGS FOR HUMAN USE

#### DRUG EFFICACY STUDY IMPLEMENTATION ANNOUNCEMENT REGARDING LUTUTRIN

The Food and Drug Administration has reviewed and evaluated a report received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations:

1. Lututrin tablets: 3,000 units of lututrin per tablet; manufactured by Hynson, Westcott & Dunning, Inc., Baltimore, Md. 21201.

2. Trexinest tablets: 500 units of lututrin and 1.0 milligram of sodium estrone sulfate per tablet; manufactured by Hynson, Westcott & Dunning, Inc., Baltimore, Md. 21201.

The Academy report states that lututrin may possibly be effective; however, the Academy also states the claims made for the drug—treatment of functional dysmenorrhea, selected cases of premature labor, and threatened and habitual abortion—are inappropriate or unwarranted in the absence of sound documentation.

The Food and Drug Administration also concludes that the claims for lututrin are inappropriate and unwarranted in the absence of sound documentation. The holder of the new-drug



applications for the drugs listed above is provided 60 days from the date of publication of this announcement in the **FEDERAL REGISTER** to submit adequate documentation, not previously submitted, in support of the representations made for the product.

The holder of the new-drug applications for these drugs has been mailed a copy of the NAS-NRC report. Any other manufacturer, packer, or distributor of such drug or any other interested person may obtain a copy of the NAS-NRC report on lututrin by writing to the Food and Drug Administration, Press Relations Office, 200 "C" Street SW., Washington, D.C. 20204.

The Commissioner of Food and Drugs invites the holders of the new-drug applications for lututrin as well as any interested person and all persons who may be adversely affected by this announcement to meet informally with officials of the Administration to discuss any medical matters relating to the conclusions regarding this drug.

Persons desiring to attend such meeting should notify the Special Assistant for Drug Efficacy Study Implementation, Bureau of Medicine, Food and Drug Administration, 200 "C" Street SW., Washington, D.C. 20204, and suitable arrangements will be made.

Any written comments on this announcement may be addressed to the Special Assistant for Drug Efficacy Study Implementation at the address given above. Comments regarding medical matters and conclusions to be discussed at the meeting should be received no later than 20 days before any meeting is held.

This notice is issued pursuant to the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050-53, as amended, 1055; 21 U.S.C. 352, 353, 371(a)) and delegated to the Commissioner (21 CFR 2.120).

Dated: May 17, 1968.

**JAMES L. GODDARD,**  
*Commissioner of Food and Drugs.*

34 F.R. 5556 (March 22, 1969)

*Food and Drug Administration*

[Docket No. FDC-D-123; NDA No. 8-986 and 10-144]

HYNSON, WESTCOTT & DUNNING, INC., LUTREXIN TABLETS,  
TREXINEST TABLETSDRUG EFFICACY STUDY IMPLEMENTATION; NOTICE OF  
OPPORTUNITY FOR HEARING

In an announcement published in the FEDERAL REGISTER of May 24, 1968 (33 F.R. 7701), the holder of the new-drug applications for drugs containing lututrin and any other interested person were invited to submit adequate documentation, not previously submitted, pertinent to the question of effectiveness for the representations made for lututrin.

The additional information received, considered together with the other information available, does not provide substantial evidence of effectiveness of lututrin for its recommended uses.

Therefore, notice is hereby given to Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, Md. 21201, and to any interested person who may be adversely affected, that the Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the following new-drug applications and all amendments and supplements thereto:

1. NDA No. 8-986 for Lutrexin Tablets; 3,000 units of lututrin per tablet.

2. NDA No. 10-144 Trexinest Tablets; 500 units of lututrin and 1.0 milligram of sodium estrone sulfate per tablet.

It is proposed to withdraw approval on the grounds that new information before the Commissioner with respect to such drugs, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence of effectiveness of the drugs in that there is a lack of substantial evidence that lututrin, a component of both drugs, has the effect or contributes to the effect

which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the applicant and any interested person who would be adversely affected by an order withdrawing such approvals an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approvals of new-drug application No. 8-986 and No. 10-144 should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing lututrin to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days from the date of publication of this notice in the **FEDERAL REGISTER**, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food, Drug, and Environmental Health Division, Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing;
- or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing the approval of these new-drug applications. Failure of such persons to file such a written appearance of election within 30 days following the date of publication of this notice in the **FEDERAL REGISTER** will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing by filing a timely written appearance of election,

a hearing examiner will be named by the Commissioner and he shall issue a written notice of the time and place for the hearing.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052, as amended; 21 U.S.C. 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: March 17, 1969.

HERBERT L. LEY, Jr.,  
*Commissioner of Food and Drugs.*

Via Registered Mail

*April 18, 1969.*

MISS BERYL S. McCULLAR,  
*Hearing Clerk, Department of Health, Education, and Welfare,  
Office of the General Counsel, Food, Drug, and Environ-  
mental Health Division, Room 5440, 330 Independence  
Avenue SW., Washington, D.C. 20201.*

DEAR MISS McCULLAR: In the Federal Register of March 22, 1969, notice was given to Hynson, Westcott & Dunning, Incorporated, that the Commissioner of Food and Drugs proposes to issue an order withdrawing approval of the new drug applications for Lutrexin Tablets (NDA No. 8-986) and Trexinest Tablets (NDA No. 10-144) on the grounds stated in the notice. The notice offered to Hynson, Westcott & Dunning, Incorporated, an opportunity for a hearing on the question of whether the new drug applications should be withdrawn.

Hynson, Westcott & Dunning, Incorporated elects to avail itself of the opportunity for a hearing.

It is our position, however, that Lutrexin Tablets and Trexinest Tablets are not new drugs under the Federal Food, Drug, and Cosmetic Act, as amended, and that, without regard to other considerations, the Drug Amendments of 1962 are not applicable to those drugs. We therefore reserve the right to contest the jurisdiction of the Commissioner and the Food and Drug Administration in the administrative proceedings, or in judicial proceedings, or in both.

Very truly yours,

HYNSON, WESTCOTT & DUNNING, INC.,

By: J. H. FITZGERALD DUNNING,

*President.*

In the United States District Court for the District of  
Maryland

Civil Action No. 21112

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, A MARY-  
LAND CORPORATION, CHARLES & CHASE STREETS, BALTIMORE,  
MARYLAND 21201, PLAINTIFF

vs.

ROBERT H. FINCH, SECRETARY OF HEALTH, EDUCATION, AND  
WELFARE, DEPARTMENT OF HEALTH, EDUCATION, AND WEL-  
FARE, WASHINGTON, D.C. 20201

AND

HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS,  
FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH,  
EDUCATION, AND WELFARE, WASHINGTON, D.C. 20201,  
DEFENDANTS

COMPLAINT FOR DECLARATORY JUDGMENT AND INJUNCTIVE  
RELIEF

Plaintiff brings this complaint (1) for a declaratory judgment that its products Lutrexin (R) Tablets and Treximest (R) Tablets (hereinafter "Lutrexin" and "Treximest") are not "new drugs" within the meaning of the definition of that term in the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Amendments of 1962 and that, even if Lutrexin and Treximest were "new drugs" within the literal meaning of that definition as so amended, they have been exempted from such amendments by specific provision of law; (2) in the alternative for a declaratory judgment that there is not a lack of substantial evidence, within the meaning of Section 505(e)(3) of the Act, that such drugs will have the effect claimed for them in their labeling; and (3) for injunctive and other relief as hereinafter set forth.

For its complaint in this cause, plaintiff alleges:

A. Defendants have proposed, in a Notice of Opportunity for Hearing, (attached hereto as Exhibit No. 1), to withdraw approval of new drug applications (NDA) for Lutrexin and Treximest on the ground that there is a lack of substantial evidence of effectiveness of the drugs and have offered plain-

tiff an opportunity for a hearing on the proposal to withdraw such approval. Defendants' proposal followed a Drug Efficacy Implementation Announcement Regarding Lututrin, in which it was stated that a National Academy of Sciences-National Research Council panel had evaluated Lutrexin and Trexineest and found lututrin, an active ingredient of the drugs, to be "possibly effective" but that the claims for lututrin are "inappropriate or unwarranted in the absence of sound documentation" (Exhibit No. 2). This evaluation, and the proposal of the Food and Drug Administration to withdraw approval of the NDAs for Lutrexin and Trexineest were made, despite the fact that new information which had become available since the NDAs were approved together with that available at the times the NDAs were approved, constitutes substantial evidence of the effectiveness of the drugs. There is no question of the safety of Lutrexin or Trexineest.

Plaintiff has elected to avail itself of the opportunity for a hearing, reserving its right to contest the jurisdiction of defendants and the Food and Drug Administration. Its letter electing to avail itself of such opportunity is attached hereto as Exhibit No. 3.

B. Lutrexin and Trexineest were regarded as "new drugs" by the Food and Drug Administration at the time new drug applications for those products were approved in 1953 and 1956, respectively, under the Federal Food, Drug, and Cosmetic Act as then in effect. Plaintiff asserts, however, that, regardless of their former status, those products were no longer "new drugs" under the Federal Food, Drug, and Cosmetic Act prior to its amendment in 1962 since, prior to such amendment, they had become "generally recognized \* \* \* as safe" for their intended uses, and that such products did not become "new drugs" by reason of the 1962 amendments, since they are generally recognized as effective for such uses; that, in any event, the products are exempt from the effectiveness requirements of the 1962 amendments; and that therefore these drugs are not subject to proceedings for withdrawal of the approved new drug applications on the ground of lack of substantial evidence of effectiveness.

C. The legal conclusion has been reached by defendants that Lutrexin and Trexineest are "new drugs" and are not ex-

empt from the Drug Amendments of 1962. It is stated in the Notice of Opportunity for Hearing that, if plaintiff (or any other interested person) fails to avail himself of the opportunity for a hearing "the Commissioner without further notice *will enter a final order withdrawing approval of these new drug applications.*" (emphasis supplied). If the products in question were no longer regarded by defendants as "new drugs" or were regarded as not subject to the effectiveness requirements of the 1962 Amendments there would be no basis for the withdrawal proceedings. Moreover, the proposal is to withdraw approval on the ground that " \* \* \* there is a lack of substantial evidence of effectiveness of the drugs \* \* \*" without regard to whether the drugs are "generally recognized" as effective by qualified experts and are therefore not "new drugs" under the statute.

D. The contemplated administrative hearing will not offer an opportunity to plaintiff to contest the jurisdiction of defendants on the ground that Lutrexin and Trexonest are not "new drugs". It would be financially and otherwise unnecessarily burdensome to require plaintiff to prepare for and participate in the administrative hearing offered by defendants before obtaining an authoritative ruling on the question of defendant's jurisdiction. The interviewing and production of witnesses to show why approvals of the new drug applications should not be withdrawn would be futile if, as plaintiff contends, defendants do not have jurisdiction over the drugs in question as "new drugs". Yet, if plaintiff should not avail itself of the opportunity for a hearing an order would be issued by defendants withdrawing approval of such applications, as a result of which plaintiff would be subjected to the threat of criminal prosecution, injunction proceedings, and seizure of the drugs, and the allegation that it was precluded from contesting such proceedings because it had failed to exhaust its administrative remedies.

E. The Commissioner could not afford plaintiff a fair and adequate hearing on the question of withdrawal of the NDAs on the ground of a lack of substantial evidence of effectiveness since he has already concluded and has testified before the Subcommittee on Intergovernmental Relations of the House of Representatives, that there is a lack of such evidence; the number and identity of the members of the NAS-NRC evaluating

panel who concurred in or dissented from its report that the products are possibly effective are unknown to plaintiff; and the Subcommittee on Intergovernmental Relations and its Chairman have improperly and coercively intruded into the adjudicatory process of FDA which has been instituted with respect to Lutrexin and Trexine. These factors deprive the contemplated hearing of even the appearance of impartiality.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,

Sep. 18, 1969.

J. H. FITZGERALD DUNNING,

*President, Hynson, Westcott & Dunning, Inc., Pharmaceutical Laboratory, Baltimore, Maryland 21201.*

DEAR MR. DUNNING: This is in further response to your letter of August 18, 1969, requesting information pertaining to the report of the Panel on Drugs Used in Disturbances of the Reproductive System, National Academy of Sciences-National Research Council, on the products Lutrexin Tablets and Trexine Tablets. Our reply to your specific requests is as follows:

1. Neither the United States Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has a Curriculum Vitae of the chairman and members of the Panel.

2. A copy of the Panel report on Trexine Tablets is enclosed.

3. Copies of the contract between the Food and Drug Administration of the National Academy of Sciences-National Research Council, Contract No. FDA 66-197 (NEG), dated April 29, 1966, and Supplemental Agreement No. 1, dated June 17, 1966, are enclosed.

4. No instructions were issued by the Food and Drug Administration or the Department of Health, Education, and Welfare other than the contract itself.

5. The Department of Health, Education, and Welfare and the Food and Drug Administration issued no instructions or guidelines to the Panel on Drugs Used in Disturbances of the Reproductive System, nor did they communicate in any way with the Panel respecting any efficacy study of any product,



including Lutrexin Tablets and Treximest Tablets. As far as this Department is aware, the only instructions to the Panel are found in the document, Guidelines for the Drug Efficacy Study of the National Academy of Sciences-National Research Council; a copy of those "Guidelines" is enclosed.

6. The Food and Drug Administration, the Consumer Protection and Environmental Health Service, and the Department of Health, Education, and Welfare do not have any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences-National Research Council Panel. The National Academy of Sciences-National Research Council Drug Efficacy Study Group may be able to inform you whether or not such documents exist.

7. Other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin and Treximest, we do not know what medical or scientific literature was relied upon by the Panel.

8. Neither the Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has any statement, other than the reports themselves, reflecting the view of each member of the Panel concerning the effectiveness of Lutrexin and Treximest.

9.-11. We have no information concerning whether the Panel solicited opinions from outside consultants, the manner in which the Panel's conclusion was reached, or whether any independent clinical studies of the effectiveness of Lutrexin and Treximest were made by the Panel or on its behalf.

12. The Food and Drug Administration has not conducted any independent clinical study or other scientific investigation of the effectiveness of Lutrexin and Treximest at any time.

13. (a) and (b) The information submitted by your firm to the Food and Drug Administration by letters dated July 22, 1968, and November 1968 was not submitted to the Panel, since the Panel had concluded its report and had it submitted to the Food and Drug Administration prior to May 23, 1968, the date and the report was sent to your firm.

(c) Your firm has elected to avail itself of the opportunity for a hearing on the question of withdrawal of approval of the

New Drug Applications for Lutrexin and Trexinvest. As you know, there is no provision for prehearing discovery in the rules of practice which govern such hearings. Written reports and memoranda prepared by Food and Drug Administration personnel prior to the issuance of the Federal Register announcement affording your firm an opportunity for a hearing on the withdrawal of the approval of the New Drug Applications for these drugs are internal-working papers which are specifically exempt from disclosure by the Public Information Act, 5 U.S.C. 552(b)(5). The official responsible for the final decision of any Food and Drug Administration action is Dr. Herbert L. Ley, Jr., Commissioner of Food and Drugs.

Sincerely yours,

(S) Morton A. Lebow,  
MORTON A. LEBOW,

*Acting Associate Director of Information for Public Services.*

DEPARTMENT OF HEALTH,  
EDUCATION, AND WELFARE,  
PUBLIC HEALTH SERVICE,  
FOOD AND DRUG ADMINISTRATION,  
*Rockville, Maryland 20852, May 19, 1970.*

NDAs 8-986; 10-144

Certified Mail Return Receipt Requested

HYNISON, WESTCOTT & DUNNING, INC.,  
*Charles and Chase Streets,  
Baltimore, Maryland 21201.*

GENTLEMEN: A Notice of Opportunity for Hearing was published in the FEDERAL REGISTER of March 22, 1969 (34 F.R. 5556) announcing that the Commissioner of Food and Drugs proposed to issue an order withdrawing approval of your new-drug applications Nos. 8-986 and 10-144 for Lutrexin Tablets and Trexinvest Tablets, respectively. Pursuant to that notice you filed an appearance electing to avail yourself of the opportunity for a hearing on that proposal.

Your attention is invited to the enclosed final order published in the FEDERAL REGISTER of May 8, 1970, promulgating Hearing Regulations and Regulations Describing Scientific

Content of Adequate and Well-Controlled Clinical Investigations. These regulations describe the scientific content of adequate and well-controlled clinical investigations and set forth the procedural requirements for requesting public hearings and demonstrating that there is a genuine and substantial issue of fact that requires a hearing.

The May 8 regulations are applicable to any request for a hearing. You should amend your request for a hearing to comply with those regulations, i.e., by submitting a well-organized and full-factual analysis of the clinical and other investigational data you are prepared to prove in a hearing, setting forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing.

Within 30 days after the date of receipt of this letter such an amendment should be filed with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-62, 5600 Fishers Lane, Rockville, Maryland 20852.

Sincerely yours,

(S) Charles C. Edwards,  
CHARLES C. EDWARDS, M.D.,  
*Commissioner of Food and Drugs.*

Enclosures.

HYNISON, WESTCOTT AND DUNNING, INCORPORATED,  
*Baltimore 1, Md., June 1, 1970.*

Office of J.H.F. DUNNING, President

Re Letter of May 19, 1970, concerning NDAs Nos. 8-986 and 10-144.

Dr. CHARLES C. EDWARDS,  
*Commissioner of Food and Drugs,*  
*Food and Drug Administration,*  
*200 C Street SW.,*  
*Washington, D.C. 20204.*

DEAR DOCTOR EDWARDS: On March 22, 1969, Dr. Herbert L. Ley, then Commissioner of Food and Drugs caused to be published in the Federal Register (34 F.R. 5556), a notice of Opportunity for Hearing on the proposal of the former Commissioner, Dr. Goddard, (33 F.R. 7701), to withdraw the new drug applications for Lutrexin and Trexinest, products marketed by Hynson, Westcott and Dunning, Incorporated (HW&D). By letter

dated April 18, 1969, HW&D filed a written appearance electing to avail itself of the offered opportunity for a hearing, reserving its right to contest the jurisdiction of the FDA over the drugs under the provisions of Section 505 of the Federal Food, Drug and Cosmetic Act, as amended.

In your letter of May 19, 1970, to HW&D, you stated that HW&D should within thirty days after receipt of the letter, file with the hearing clerk an "amendment" of its "request" for a hearing on the proposal to withdraw the new drug applications for Lutrexin and Trexonest, and that the "request" as amended should comply with the newly issued substantial evidence regulations of May 8, 1970, which set forth new conditions for obtaining a hearing and new provisions purporting to define the term "adequate and well-controlled investigations", as used in the definition of "substantial evidence" in Section 505(d) of the Act. Thus, you stated that the "amended request" should set forth "specific facts showing that there is a genuine and substantial issue of fact that requires a hearing".

HW&D respectfully declines to submit any further appearances or a "request" for a hearing, on the grounds that the company is entitled to a hearing under the Act and has complied with the regulations of the FDA concerning the right to a hearing which were in effect when it accepted the offer of a hearing made by Commissioner Ley. Moreover, in your letter to me (undated) received on May 14, 1970, it was stated that the data submitted by HW&D "do not provide substantial evidence of effectiveness" of Lutrexin and Trexonest. Since the matter has already been judged, we can see no value in following the course which you suggest in your letter of May 19, entirely aside from the question of the validity of the regulations as applied to Lutrexin and Trexonest.

As you are aware, HW&D has filed an action against the Secretary of HEW and the Commissioner of Food and Drugs for a declaratory judgment and injunctive relief (Civil Action No. 21112, United States District Court for the District of Maryland). If HW&D should prevail in that proceeding the question of whether a hearing should be held by FDA would be moot.

On May 26, 1970, counsel for HW&D and the Government met informally with Judge Northrop of the United States Dis-

trict Court in Baltimore. Judge Northrop set the hearing on the Government's motions to dismiss and for summary judgment in the action brought by HW&D, for September 4, 1970. Mr. Goodrich, representing the Food and Drug Administration, stated that while FDA would not agree to an injunction prohibiting government action against plaintiff or its products pending disposition of the motions in the Baltimore action, the agency would not, pending such disposition, undertake proceedings looking to withdrawal of the NDAs for Lutrexin and Trexinest under Section 505(e)(3) of the Act.

Very truly yours,

Hynson, Westcott & Dunning, Inc.  
(S) By: J. H. Fitzgerald Dunning,  
J. H. FITZGERALD DUNNING.

### *Order of Dismissal*

This case came on for argument on September 4, 1970, on the defendants' motion to dismiss and in the alternative for summary judgment, and counsel for the parties having been heard, first on the plaintiff's motion for continuance and then on defendants' motion for dismissal and the court being fully advised, it is this 16th day of September, 1970.

Ordered, that the motion for continuance is denied on the ground that the case was set for argument several weeks ago and contrary to the plaintiff's representations there is no cause for delay based upon new arguments advanced by the defendants, and it is further

Ordered, that the defendants' alternative motion for summary judgment is denied, and that the defendants' motion for dismissal is granted, for the reasons that the issues presented to the court are within the primary jurisdiction of the Secretary of Health, Education, and Welfare, the plaintiff has failed to exhaust its administrative remedies through which the plaintiff will be enabled to obtain an Agency determination on the record made before the Agency on the medical issues involved, on its claim that the drugs involved are generally recognized among qualified experts as safe and effective for their intended uses, its claim that they are protected from the drug efficacy review by the Grandfather Clause of the 1962 Amendments, and the claim that there is substantial evidence available to

support the therapeutic effectiveness for which the drugs are promoted. Review of the final Agency action will be available in the Courts of Appeals.

The Clerk is directed to withdraw the Order of Sept. 11th 1970 filed herein and file this Order in lieu thereof.

Edward S. Northrop  
Judge EDWARD S. NORTHROP.

Date:

(Certificate of Service Omitted in Printing)

HARTER, CALHOUN & WILLIAMS,  
423 WASHINGTON BUILDING,  
Washington, D.C. 20005, October 16, 1970.

DOW W. HARTER,  
LEONARD J. CALHOUN (1963),  
EDWARD BROWN WILLIAMS,  
JAN EDWARD WILLIAMS,  
(202) 628-3733.

Re Docket No. FDC-D-123; NDA No. 8-986 and 10-144.

MISS BERYL McCULLAR,  
*Hearing Clerk, Food and Drug Administration,  
Department of Health, Education, and Welfare,  
Room 6-62, 5600 Fishers Lane, Rockville, Maryland 20852.*

DEAR MISS McCULLAR: By Notice published in the Federal Register of March 22, 1969, (34 F.R. 5556), the Commissioner of Food and Drugs offered Hynson, Westcott and Dunning, Incorporated (HW&D) an opportunity for a hearing on the proposal (33 F.R. 7701) of the Commissioner to withdraw the new drug applications for HW&D's Lutrexin tablets (NDA No. 8-986) and Trexine tablets (NDA No. 10-144). By letter dated April 18, 1969, HW&D elected to avail itself of the opportunity for a hearing. Under the regulations of the Food and Drug Administration, HW&D had met all the requirements for an administrative hearing. Under 21 CFR 130.14(b), a hearing was to be held within 90 days after HW&D's election to accept it, unless the parties agreed otherwise.

HW&D stated in its letter, however, that "Lutrexin tablets and Trexine tablets are not new drugs under the Federal Food, Drug, and Cosmetics Act, as amended, and without regard to

other considerations, the Drug Amendments of 1962 are not applicable to those drugs. We therefore reserve the right to contest the jurisdiction of the Commissioner and the Food and Drug Administration in the administrative proceedings or in judicial proceedings or in both."

Thus, on August 19, 1969, HW&D filed a complaint for declaratory judgment and injunctive relief in the United States District Court for the District of Maryland (*Hynson, Westcott and Dunning, Incorporated vs. Finch*, C.A. No. 21112), seeking a judicial determination of the following questions: (1) whether the drug products were generally recognized as safe on or before October 9, 1962, and if so, are they for that reason exempt from the effectiveness provisions of the 1962 Amendments under the Grandfather Clause of those Amendments; and (2) whether in any event these drugs are now generally recognized as both safe and effective and for that reason are not new drugs under the definition in Section 201(p) of the Federal Food, Drug, and Cosmetic Act. No further action was taken pursuant to HW&D's April 18, 1969, election to avail itself of an opportunity for a hearing.

After a hearing in open court, Judge Northrop of the Maryland District Court on September 11, 1970, dismissed HW&D's suit on the ground that the issues presented to the court were within the primary jurisdiction of the Secretary of HEW and that HW&D had failed to exhaust its administrative remedies. The Order, a certified copy of which is attached hereto and made a part hereof, specifically provided that HW&D's administrative remedies would enable it to "obtain an agency determination on the record made before the Agency on the medical issues involved, on its claim that the drugs involved are generally recognized among qualified experts as safe and effective for their intended uses, its claim that they are protected from the drug efficacy review by the Grandfather Clause of the 1962 Amendments, and the claim that there is substantial evidence available to support the therapeutic effectiveness for which the drugs are promoted. Review of the final Agency action will be available in the Court of Appeals."

Pursuant to the Order of the court in *Hynson, Westcott and Dunning, Incorporated vs. Finch*, HW&D hereby requests that the Commissioner of Food and Drugs initiate the procedures

for an administrative hearing pursuant to Part 130.14 et seq. as constituted at the time of acceptance by HW&D of an opportunity for a hearing (April 18, 1969), whereby a hearing will be held on the question of the proposal of the FDA to withdraw the new drug applications for Lutrexin and Trexonest on the ground that new information before the Commissioner with respect to such drugs, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence of effectiveness of the drugs.

Further, pursuant to the Order of the court in *Hynson, Westcott and Dunning, Incorporated vs. Finch*, a hearing is requested on the following questions which the court held were within the primary jurisdiction of the FDA and must be determined on the record by the agency:

(1) Whether after the new drug applications (NDAs) for Lutrexin and Trexonest became effective in 1953 and 1956 respectively, those drugs became, prior to October 10, 1962, generally recognized by qualified experts as safe for use under the conditions stated in their labeling and have been used to a material extent and for a material time under such conditions (other than in investigations to determine their safety and effectiveness), within the meaning of Section 201(p) of the Federal Food, Drug, and Cosmetic Act, and are for that reason exempt from the Drug Amendments of 1962, by the Grandfather Clause contained in Section 107(c) of the Amendments.

(2) Whether Lutrexin and Trexonest are now generally recognized by qualified experts as safe and effective for use under the conditions stated in their labeling and have been used to a material extent and for a material time under such conditions (other than in investigations to determine their safety and effectiveness), within the meaning of the definition of new drugs contained in Section 201(p) of the Federal Food, Drug, and Cosmetic Act as amended.



### *I. Substantial Evidence—Supporting Data*

The data listed below have heretofore been submitted to FDA pursuant to the Drug Efficacy Study Implementation Announcement (33 F.R. 7701), in support of HW&D's position that there is substantial evidence of effectiveness of Lutrexin for its indicated uses, and such data is incorporated herein by reference:

1. Data submitted in connection with New Drug Application for Lutrexin tablets which became effective in 1953.

2. August 20, 1965—Dr. J. H. F. Dunning's letter to Mr. G. P. Larrick, Commissioner, re Lutrexin literature being submitted to Drug Efficacy Study Group of NAS-NRC.

*Enclosures:*

- (a) Lutrexin labelling.
- (b) Lutrexin package insert.
- (c) Lutrexin bibliography.
- (d) Lutrexin published reprints and abstracts.
- (e) Lutrexin New and Non-Official Remedies Publications, 1955 to 1962.

3. August 20, 1965—Dr. J. H. F. Dunning's letter to Mr. G. P. Larrick, Commissioner, re Treximest literature being submitted to Drug Efficacy Study Group of NAS-NRC.

*Enclosures:*

- (a) Treximest labelling.
- (b) Treximest package insert.
- (c) Treximest published reprints and abstracts.

4. August 30, 1966—Dr. C. A. Dunning's letter, with NAS Drug Efficacy Study Form on Treximest Tablets.

5. September 6, 1966—NAS Submission.

*Enclosures:*

- (a) Rizzolo reprint, "A Uterine Relaxant for Premature Uterine Contractions".
- (b) Lutrexin bibliography.
- (c) Supporting letter on Lutrexin from Dr. Braun, Sheboygan Clinic, Sheboygan, Wisconsin.

6. July 12, 1968—Messrs. John K. Worley/Bruce J. Brennan's letter to Dr. Paul A. Bryan, responding to Drug efficacy Study Implementation Announcement published in the Federal Register, May 24, 1968.

7. July 18, 1968—Messrs. Bruce J. Brennan/John K. Worley's letter to Dr. H. L. Ley, re submitting data within time period set forth in May 24, 1968, Announcement.

*Enclosure:*

Messrs. Worley/Brennan's letter of July 12.

8. July 22, 1968—Mr. G. F. Whattam's letter to Dr. Paul A. Bryan re consideration of extension until September 15, 1968.

*Enclosures:*

(a) Dr. Grattons' paper.

(b) Jeremias & Trythall paper, April 1962 Meet. of Inter. Fertility Assoc.

(c) Curriculum vitae on Drs. Gratton, Majewski, Rezek, and Trythall.

9. July 26, 1968—Messrs. Bruce J. Brennan/John K. Worley's letter to Dr. H. L. Ley, Jr., re FDA's refusal to grant HW&D request for extension. Request for reconsideration.

10. November 22, 1968—Lutrexin Submission to FDA.

*Enclosures:*

(a) Dr. J. H. F. Dunning's letter to Commissioner G. P. Larrick of August 20, 1965, re Lutrexin.

(b) Dr. J. H. F. Dunning's letter to Commissioner G. P. Larrick of August 20, 1965, re Trexine.

(c) Curriculum vitae on Dr. R. L. DiBenedetto, Baton Rouge, Louisiana.

(d) Paper by Dr. DiBenedetto, "Treatment of Premature Labor in Clinic Patients".

(e) Curriculum vitae on Dr. F. B. Gray, Grand Rapids, Michigan.

(f) Paper by Dr. Gray, "Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases".

(g) Curriculum vitae on Dr. J. T. Majewski, Milwaukee, Wisconsin.

(h) Paper by Dr. Majewski, "Statistical Evaluation in the Reduction of the Incidence of Prematurity".

(i) Curriculum vitae on Dr. G. H. Rezek, Cicero, Illinois.

(j) Paper by Dr. Rezek, "A Summary of Case Findings Over a 10 Year Period".

(k) Curriculum vitae on Dr. R. W. Vera, Southfield, Michigan.

(l) Lutrexin Case Records by Dr. Vera, "The Use of Lutrexin in Reducing Uterine Irritability and Neonatal Deaths Caused by Premature Labor. A Description of 22 Cases".

(m) Paper by Dr. John W. Huffman, Chicago, "From Menarche to Maturity. A Gynecologist's Approach", Postgraduate Medicine, June 1968.

(n) Paper by Dr. G. H. Rezek, "Uterine Motility and the Survival of the Fetus", Medical Digest Bombay 4, July 1963.

(o) Supporting letters from: Dr. J. R. Allan, Excelsior Springs, Missouri; Dr. R. G. Barrick, Chicago, Illinois; Dr. W. M. Bickers, Beirut, Lebanon; Dr. B. D. Coleman, Augusta, Georgia; Dr. E. A. Chandler, Houston, Texas; Dr. I. Goldberg, Augusta, Georgia; Dr. H. A. Bollin, Chicago, Illinois; Dr. Bernard Gomborg, Bellevue, Washington; Dr. H. Hoffman Groskloss, Miami, Florida; Dr. J. M. Haws, Baltimore, Maryland; Dr. Grey Jones, St. Louis, Missouri; Dr. R. A. McDermott, Jr., Chicago, Illinois; Dr. P. H. Muskie, Dearborn, Michigan; Dr. G. P. Nolan, Westminster, California; Dr. W. F. Peterson, USAF, Andrews AFB, Washington, DC; Dr. C. L. Randall, Buffalo, New York; Dr. H. A. Ritter, St. Louis, Missouri; Dr. R. T. F. Schmidt, Cincinnati, Ohio; Dr. M. D. Sims, South Miami, Florida.

11. April 18, 1969—Dr. J. H. F. Dunning's letter to Miss B. S. McCullar, Hearing Clerk, Office of General Counsel, electing opportunity for a hearing.

It is submitted that these data constitute substantial evidence of the effectiveness of Lutrexin for its indicated uses. HW&D is entitled to a hearing under the regulations as framed on April 18, 1969, and has fully complied with the requirements of those regulations. It is our position that the May 8, 1970, substantial evidence regulations cannot legally be

applied to this proceeding, and that the regulations are legally invalid in many crucial respects. Assuming, *arguendo*, their applicability, however, the data listed above constitute "substantial evidence" as defined in the May 8, 1970 regulations and are legally sufficient to warrant the holding of an administrative hearing on the question of the substantial evidence of Lutrexin.

In any event, the new evidence in the form of affidavits and other data, attached hereto and listed under Part 2 herein, clearly demonstrate that there is substantial evidence of effectiveness of Lutrexin under the May 8, 1970 regulations. This evidence at the least requires that the FDA hold a hearing on its proposal to withdraw the new drug application for Lutrexin.

## II. Jurisdictional Questions—Supporting Data

The following data are submitted in support of HW&D's request for a hearing on the jurisdictional questions posed above. With the exception of the affidavit of Dr. Sylvester W. Trythall, the data were before the court in *Hynson, Westcott and Dunning, Inc. vs. Finch*.

This request for a hearing on the jurisdictional issues is made pursuant to the Court's Order in the *Finch* case. The hearing would involve substantive questions of fact concerning general recognition of safety and effectiveness. These factual questions can only be decided on the record after an adjudicatory hearing before the Food and Drug Administration. The matters of substantial evidence and the applicability of the May 8, 1970 regulations are relevant only to the hearing requested under Part I of this letter and not to this request for a hearing on the jurisdictional questions. We can therefore see no basis for denial of this request. If Luxtrexin were, after a hearing, found not to be a "new drug", or not to be subject to the Drug Amendments of 1962, the questions of substantial evidence and the applicability of the May 8, 1970 regulations would be moot.

A listing of the data submitted herewith follows:

1. HW&D's Complaint for Declaratory Judgment and Injunctive Relief in *Hynson, Westcott and Dunning, Incorporated vs. Finch*, CA No. 21112, including three exhibits: Drug Efficacy Study Implementation (33 F.R.

7701), Notice of Opportunity for Hearing (34 F.R. 5556), and letter of HW&D electing to avail itself of opportunity for a hearing, dated April 18, 1969.

2. HW&D's Memorandum in Opposition to Defendants' Motions to Dismiss and in the Alternative for Summary Judgment (CA No. 21112), with the following exhibits:

(a) Exhibit I. Affidavit of William M. Bickers, M.D., with curriculum vitae (Exhibit A) and list of publications.

(b) Exhibit II. Affidavit of Richard R. Gratton, M.D., with curriculum vitae (Exhibit A) and a true copy of paper by Dr. Gratton entitled "Treatment of Infertility and Prematurity Pregnancy Problems".

(c) Exhibit III. Affidavit of Fred B. Gray, M.D., with clinical report entitled: "Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases".

(d) Exhibit IV. Affidavit of Joseph T. Majewski, M.D., with curriculum vitae and list of publications (Exhibit A), and true copies (Exhibits B, C, and D) of papers by Dr. Majewski, entitled: "A Uterine Relaxing Factor for Premature Labor", "Further Experiences with a Uterine-Relaxing Hormone in Premature Labor", and "Statistical Evaluation in the Reduction of the Incidence of Prematurity".

(e) Exhibit V. Affidavit of George H. Rezek, M.D., with curriculum vitae and list of publications (Exhibit A), and true copies of two pages (Exhibits B and C) by Dr. Rezek entitled: "The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea" and "Lutrexin in the Treatment of Premature Labor".

(f) Exhibit VI. Affidavit of Joseph F. Sadusk, M.D., with curriculum vitae (Exhibit A), list of publications (Exhibit B), and true copy of paper Exhibit C) by Dr. Sadusk entitled: "The Definition of the Efficacy of a Drug Under the Law".

(g) Exhibit VII. Copy of letter dated January 22, 1970, from HW&D to Commissioner Edwards, with copy of letter dated December 10, 1969, from Willard

M. Allen, M.D., to J. H. F. Dunning, President of HW&D (Exhibit A).

(h) Exhibit VIII. Commissioner Edwards' reply, undated, to Dr. Dunning's letter of January 22, 1970.

3. Copy of Motion of Plaintiff for Continuance.

4. Affidavit of Sylvester W. Trythall, M.D., dated September 14, 1970, with curriculum vitae and list of publications.

5. Letter dated May 19, 1970, from Commissioner Edwards to HW&D.

6. Letter dated June 10, 1970, from J. H. F. Dunning to Commissioner Edwards.

7. True copy of Transcript of Hearing on Defendants' Motions to Dismiss and in the Alternative for Summary Judgment in CA No. 21112 (D. Md.), on September 4, 1970.

8. Certified copy of Order of Dismissal in CA No. 21112 (D. Md.), September 11, 1970.

Respectfully submitted,

(s) Edward Brown Williams  
EDWARD BROWN WILLIAMS,  
*Counsel for Hynson, West-*  
*cott and Dunning, Incorporated.*

EBW: fh.  
Enclosures.

*Affidavit of William M. Bickers, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment*

William M. Bickers, being duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in opposition to defendants' motion to dismiss and in the alternative for summary judgment, filed herewith in the above-captioned cause.

2. I am a physician engaged in the practice of obstetrics and gynecology in Richmond, Virginia, and Beirut, Lebanon. I received an M.D. degree from The Medical College of Virginia

in 1933, and was licensed to practice medicine in Virginia in 1933. I am a Diplomate of the American Board of Obstetrics and Gynecology, the American Fertility Society, and the Society for the Study of Sterility.

3. I am presently, and have been since 1960, professor and chairman of the Department of Obstetrics and Gynecology, The American University Hospital, Beirut, Lebanon. I spend nine months of the year in Beirut and two to three months in Richmond, Virginia, where I, with my associate, maintain an active OB/GYN practice. I have authored approximately fifty-eight papers dealing with obstetrics and gynecology as well as two textbooks on the subject. A copy of my curriculum vitae is attached hereto as Exhibit A. I am familiar with the scientific literature in the OB/GYN field including that concerning Lutrexin, and keep myself currently informed by the study of such literature, attendance at meetings of professional societies, and consultation with OB/GYN specialists.

4. I commenced using Lutrexin Tablets for dysmenorrhea, and second and third trimester threatened abortion in 1953, and have used the drug for these indications in my practice in Richmond up to the present time. Hynson, Westcott & Dunning, Incorporated does not have a representative in Beirut, and consequently, Lutrexin is not available there. I have in my practice prescribed Lutrexin for over three hundred patients with pregnancy problems, and over one thousand patients with dysmenorrhea.

5. Clinical experience such as my own in the use of Lutrexin in treatment of dysmenorrhea and premature labor, as well as studies such as those preformed by Drs. J. T. Majewski and G. H. Rezek (Majewski and Jennings: *Uterine Relaxing Factor for Premature Labor*, OB & GYN., 5:649-652, May 1955, and *Further Experiences with a Uterine Relaxing Hormone in Premature Labor*, OB & GYN., 9:322-325, March, 1957; Rezek, *The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea*, AM. J. OB & GYN., 66:396-402, August, 1953, and *Lutrexin in the Treatment of Premature Labor*, Annals of New York Academy of Sciences, 75:995-997, January, 1959) show the effectiveness and safety of Lutrexin and cannot be ignored on the ground they are not double-blind placebo type investigations. The

difficulties concomitant with the performance of this type of study of a drug for use in conditions with a high risk of fatality are well known. Accordingly, clinical studies of the type cited, together with clinical experience must, of necessity, be considered.

6. I have studied the report of the panel of the National Academy of Sciences-National Research Council which evaluated Lutrexin as "possibly effective" in the treatment of dysmenorrhea and threatened abortion, and understand that the Food and Drug Administration, subsequent to the report, has proposed to remove Lutrexin from the physician's armamentarium. I have also reviewed the data of Hynson, Westcott and Dunning, Incorporated submitted to the Food and Drug Administration in response to the proposed removal of the drug from the market.

7. Based upon my experience in obstetrics and gynecology and with the use of Lutrexin in that practice, set forth above, it is my opinion that the drug is therapeutically effective in the treatment of dysmenorrhea and second and third trimester threatened abortion. Further, the safety of Lutrexin is subject to no question; I have prescribed up to four tablets per day (12,000 units) for dysmenorrhea and labor difficulties, and have found no side effects of any significance whatever. Lutrexin is a valuable drug in these cases and is the only effective agent available to the OB/GYN practitioner faced with the problem of an excessively irritable uterus.

8. Based upon my experience, summarized above, discussions with OB/GYN colleagues, and upon my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as safe and effective for use in the treatment of cases of dysmenorrhea and second and third trimester threatened abortion under the conditions recommended in its labeling. Upon the same basis it is my opinion that the safety of Lutrexin has been generally recognized by such physicians for such uses for at least ten years.

I am prepared to testify as to these matters in court.

(S) William M. Bickers

WILLIAM M. BICKERS, M. D.



REPUBLIC OF LEBANON, CITY OF BEIRUT,  
EMBASSY OF THE UNITED STATES OF AMERICA, ss:

Subscribed and sworn to before me Thomas B. Killeen, Vice  
Consul of the United States of America, at Beirut, Lebanon,  
duly commissioned and qualified on 12th day of March, 1970.

(S) Thomas B. Killeen,  
THOMAS B. KILLEEN,  
American Vice Consul.

Date: March 12, 1970.

[Exhibit A]

### PROFESSIONAL STATISTICS

DR. WILLIAM M. BICKERS, *412 Medical Arts Building, Richmond, Virginia 23217.*

Year of Birth: 1908.

Medical Education: Medical College of Virginia, Richmond,  
M.D. Degree, 1933.

Year of License: 1933, State of Virginia.

American Specialty Board: American Board of Obstetrics and  
Gynecology.

Primary Specialty: Obstetrics and Gynecology.

Type of Practice: Full time specialty practice.

Internship: 1933-34, Medical College of Virginia.

Residency: Obstetrics & Gynecology, Boston City Hospital,  
1934-35.

Professorial Appointment: Instructor, Gynecology, Medical  
College of Virginia, 1936-49.

Professor and Chairman of the Department of Obstetrics &  
Gynecology, American University, Beirut, 1945-46, 1960—

Professional Societies:

American Medical Association.

American Association of Obstetrics & Gynecology.

American Fertility Society.

American Association for the Advancement of Sciences.

Endocrinology Society.

Society for the Study of Sterility.

Pan-am. Cancer Cytol. Soc. Endocrinology.

Society for the Study of Uterine Muscle Physiology.

*Affidavit of Richard R. Gratton, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment*

Richard R. Gratton, M.D., being first duly sworn, deposes and says:

1. I received an M.D. degree from the Stanford University School of Medicine, Palo Alto, California in 1944, and was licensed to practice medicine in California in 1947. My primary specialty is obstetrics and gynecology. I am a fellow of the American College of Obstetricians and Gynecologists, a member of the American Society of Abdominal Surgeons, and a past member of the International Fertility Association. A copy of my curriculum vitae is attached hereto as Exhibit A.

2. My practice deals primarily with what may be termed a subspecialty of OB/GYN practice, i.e., the treatment of infertility or habitual abortion. The majority of the patients I treat are pregnant women (or those who contemplate pregnancy), who have been referred to me by other physicians and who have a history of from one to ten previous miscarriages, spontaneous abortions, or premature deliveries. I have been engaged in this specialty for nineteen years, and have treated one thousand and thirty-six patients for this affliction. I am familiar with the scientific literature in OB/GYN, including that concerning Lutrexin, and keep myself currently informed by the study of such literature, attendance at meetings of professional societies, and consultation with OB/GYN specialists.

3. I have had extensive experience in the use of Lutrexin tablets manufactured by Hynson, Westcott and Dunning, Inc., having administered the drug to more than one thousand women with a history of pregnancy complications, over a period of fourteen years. I have attached hereto as Exhibit B a copy of my paper entitled *The Treatment of Infertility and Prematurity Pregnancy Problems* (1968, unpublished). In this study are reported the results of Lutrexin therapy in 219 habitual aborters.

4. I have reviewed the report of the panel of the National Academy of Sciences-National Research Council which evalu-

ated Lutrexin as "possibly effective" in treatment of premature labor and habitual abortion, and I have been informed that the Food and Drug Administration has, because of the report, proposed to remove Lutrexin from the market. I have also reviewed the data of Hynson, Westcott and Dunning, Inc. submitted to FDA in response to the proposed removal of the drug from the market.

5. Based on my experience with Lutrexin, above-outlined, it is my opinion that Lutrexin is an effective agent in the treatment of habitual abortion and premature labor. Moreover, there is no question that Lutrexin is safe, for I have administered up to 36,000 units of the drug to many patients in an eight to twenty-four-hour period with no side effects to mother or child. It is my firm belief that removal of Lutrexin from the physician's armamentarium would be a grievous error. Lutrexin has proved invaluable to me in my practice which involves patients who have repeatedly faced the tragedy of premature expulsion of a non-viable fetus. Although progestational agents are useful in the first trimester of pregnancy, there is no product other than Lutrexin which is effective in producing quiescence of the uterus in the second and third trimester of pregnancy as well as in the first trimester. As stated in the attached study, prior to institution of the use of Lutrexin as the major drug in treating infertility cases, less than 50 per cent viable babies resulted. With the use of Lutrexin 80 per cent viable babies were obtained.

6. Studies such as the one reported in Exhibit B, utilizing the past histories of the patients as controls, together with the clinical experience of the physician, are proof of the effectiveness of Lutrexin. Such studies of and experience with a drug cannot be dismissed on the ground that they are valueless because they do not use a double-blind placebo type of investigation. The latter type of investigation is inconceivable from the standpoint of ethics and morality where, as here, there exists a high risk of mortality and the physician is testing a drug (Lutrexin) which is clinically-proven to be effective.

7. Based upon my experience, summarized above, discussions with OB/GYN colleagues and my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as safe and effective for use in the treatment of cases of habitual abortion and premature labor under

the conditions recommended in its labeling. Upon the same basis, it is my opinion that the safety of Lutrexin has been generally recognized by such physicians for such uses for at least ten years.

8. I am prepared to testify as to these matters and give supporting data to my opinions expressed above in a proceeding in court or at a hearing before the Food and Drug Administration.

(S) Richard R. Gratton, M.D.  
RICHARD R. GRATTON, M.D.

Subscribed and sworn to before me this 12th day of March, 1970.

(S) MARJORIE S. HAMBURGER,  
*Notary Public*

[Exhibit A]

# PROFESSIONAL STATISTICS

DR. RICHARD R. GRATTON,  
490 Post Street,  
San Francisco, California 94102

Year of Birth: 1915.

Medical Education: Stanford University School of Medicine,  
Palo Alto, California, M.D. Degree in 1944.

Year of License: 1947.

Primary Specialty: Obstetrics and Gynecology.

Type of Practice: Full time specialty practice.

Internship and Residence:

U.S. Naval Hospital, Mare Island, California 1943-44.

All Ob-Gyn Interne 1947-48.

Assistant Resident 1948-49.

Senior Assistant Resident 1949-50.

Resident 1950-51, Stanford University Hospital.

Teaching Affiliation:

Teaching Assistant Ob/Gyn, Sanford Medical School.

Lecturer in Ob, Stanford School of Nursing.

Hospital Affiliation:

Stanford University Hospital.

St. Francis Memorial Hospital.

Childrens Hospital.

St. Joseph Hospital.  
 St. Marys Hospital.  
 Franklin Hospital.

Membership:

American College of Obstreticians and Gynecologists.  
 American Society of Abdominal Surgeons.

Papers:

Haman, J. O. and Gratton, R. R.; The Obstreticians Responsibility to the Previously Infertile Patient, Proceedings of the Second World Congress on Fertility & Sterility, 1956.

Gratton, R. R., and Thelander, H. E.: A Developmental Study of Triplets, Journal Amer. Med. Wom. Assoc. 16: 445-9, June 1961.

Gratton, R. R.: The Treatment of Infertility and Prematurity Pregnancy Problems, (1968 Unpublished).

The undersigned hereby certifies that the foregoing is a true and correct statement of his professional qualifications.

(S) Richard R. Gratton, M.D.  
 RICHARD R. GRATTON, M.D.

Date 6 March 1970.

*Affidavit of Joseph T. Majewski, M.D., in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment*

Joseph T. Majewski, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in opposition to defendants' motion to dismiss and in the alternative for summary judgment, filed herewith in the above-entitled cause.

2. I received an M.D. degree from Marquette University School of Medicine in 1945, and was licensed to practice medicine in Wisconsin in 1948. My specialty is obstetrics and gynecology and I am certified by the American Board of Obstetrics and Gynecology. I am also a fellow of the American College

of Obstetricians and Gynecologists. A copy of my curriculum vitae is attached hereto as Exhibit A.

3. I have engaged in the active practice of obstetrics and gynecology for eighteen years, and have used Lutrexin in the treatment of cases of threatened abortion and premature labor for more than fourteen years. I have administered Lutrexin to more than three hundred women to prevent premature delivery of the infant. I am familiar with the scientific literature dealing with threatened abortion and premature labor, including that concerning Lutrexin. I keep myself currently informed by the study of such literature, attendance at meeting of professional societies, and consultation with colleagues.

4. I have written three papers (copies of which are attached hereto as exhibits) reported the results of administration of Lutrexin in cases of premature labor, viz., (Exhibit B) Majewski and Jennings, *A Uterine Relaxing Factor for Premature Labor*, *Obstetrics and Gynecology*, Vol. 5, No. 5, 649 (May, 1955); (Exhibit C) Majewski and Jennings, *Further Experiences With A Uterine Relaxing Hormone in Premature Labor*, *Obstetrics and Gynecology*, Vol. 9, No. 3, 322 (March, 1957); and (Exhibit D) Majewski, *Statistical Evaluation in the Reduction of the Incidence of Prematurity* (1968, unpublished).

5. I have reviewed the report of the panel of the National Academy of Sciences-National Research Council which found Lutrexin to be "possibly effective" in the treatment of threatened abortion and premature labor, and understand that the Food and Drug Administration has moved to take Lutrexin off the market, subsequent to this "possibly effective" evaluation. In addition, I have reviewed the data of Hynson, Westcott and Dunning submitted to FDA in response to the proposed removal of Lutrexin from the market.

6. It is my opinion, based upon my experience with Lutrexin, the pertinent scientific literature, and the contacts mentioned in paragraph 3 above, that Lutrexin is effective in the treatment of cases of threatened abortion and premature labor. I have found, in my practice, no other effective therapeutic agent for these indications. The safety of Lutrexin, not only in the dosage suggested in the drug's labeling but in amounts substantially in excess thereof, is beyond dispute. I have frequently administered 4000 units of the drug stat., and 1000 units hourly thereafter

until Uterine contractions cease, and have never encountered any adverse effects in either mother or infant. Removal of Lutrexin from the OB/GYN's armamentarium would in my opinion border on the criminal, for, as shown in my 1968 study (Exhibit D), before treatment with Lutrexin, 75 patients, with 210 pregnancies, delivered only 109 live infants (52 per cent). The same 75 women on Lutrexin therapy produced 65 live children out of a total of 75 pregnancies (86 per cent).

7. The method of investigation utilized in my studies (Exhibit B, C, and D) *viz.*, use of the patients as their own controls, or use as a control of statistics reflecting the experience with other patients with no treatment, together with the general clinical experience of the physician, constitute the only humane approach to the study of the effectiveness of a drug for use in threatened abortion and premature labor. These complications of pregnancy carry a high risk to the life of the fetus and perhaps the mother. Use under such conditions of a double-blind, placebo type of investigation would be unethical and immoral, where, as here, there exists a drug (Lutrexin) clinically-proven to be of value in the treatment of the affliction involved.

8. Based upon my experience, communications with OB/GYN practitioners in Wisconsin and elsewhere concerning Lutrexin and upon my knowledge of the literature relating to the drug and the conditions of its use, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as both safe and effective in treatment of threatened abortion and premature labor under the conditions of use recommended in its labeling. Upon the same basis it is my opinion that the safety of Lutrexin has been generally recognized for such use under such conditions by OB/GYN physicians for at least ten years.

9. I am prepared to testify as to these matters, and to present data to support the opinions expressed above, in a proceeding in court or before the Food and Drug Administration.

/s/ Joseph T. Majewski, M.D.

JOSEPH T. MAJEWSKI, M.D.

Subscribed and sworn to before me this 5th day of March, 1970.

(S) JOHN G. MALONEY,

Notary Public,

Comm. Exp. 10-4-70.

[Exhibit A]

## PROFESSIONAL STATISTICS

Name: Joseph T. Majewski.

Office Address: 10425 West North Avenue, Milwaukee, Wisconsin.

Date of Birth: 1922, Milwaukee, Wisconsin.

Curriculum Vitae:

1945, M.D. degree, Marquette University School of Medicine, Milwaukee, Wisconsin.

1945-46, Intern, U.S. Navy Hospital, Farragut, Idaho.

1946-48, Lt. (jg) USNR.

1948-51, Resident, Lewis Memorial Maternity Hospital.

19—, Clinical Instructor, Department of Obstetrics and Gynecology, Marquette, University School of Medicine.

19—, Att. Staff, St. Joseph Hospital and Evangelical Deaconess Hospital, Milwaukee, Wisconsin; Courtesy Staff, Milwaukee Hospital; Att. Staff, Milwaukee County General Hospital.

Certification: 1948, License to practice medicine 1955, American Board of Obstetrics and Gynecology.

Private Specialty: Obstetrics and Gynecology.

Type of Practice: Full-time specialty practice.

Membership in Professional Societies:

American Medical Association.

American Association of Obstetrics and Gynecology.

Central Association of Obstetrics and Gynecology.

American College of Obstetricians and Gynecologists.

Papers:

Majewski, J.: Stab Wounds of Heart; 2 cases, Polski Tygodnik Lek, 2:390-393, 1947.

Schmitz, H. E. and Majewski, J. T.: End Results in Treatment of Ovarian Carcinoma With Surgery and Deep X-Ray Irradiation, Radiology, 57:820-825, December 1951.

Majewski, J. T. and Jennings, T.: Uterine Relaxing Facts for Premature Labor, Obst. & Gynec., 5:659-652, May 1955.

Majewski, J. T. and Jennings, T.: Further Experience with a Uterine-Relaxing Hormone in Premature Labor, Obst. & Gynec., 9:322-325, March 1957.



Majewski, J. T.: Statistical Evaluation in the Reduction of the Incidence of Prematurity, 1968, unpublished.

#### CERTIFICATE

The undersigned hereby certifies that the foregoing is a true and correct statement of his professional qualifications.

(S) J. T. Majewski, M.D.  
J. T. MAJEWSKI, M.D.

Date: March 5, 1970.

*Affidavit of George H. Rezek, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment*

George H. Rezek, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in opposition to defendants' motion to dismiss and in the alternative for summary judgment, filed herewith in the above-entitled cause.

2. I am a physician engaged in the practice of obstetrics and gynecology in the State of Illinois. I received an M.D. degree from the University of Illinois in 1932, and am licensed to practice medicine in that State. I am a Diplomate of the American Board of Obstetrics and Gynecology and a Fellow of the American College of Obstetricians and Gynecologists, the American College of Surgeons and The International College of Surgeons. I am also a member of the Chicago Gynecological Society. A copy of my curriculum vitae is attached hereto (Exhibit A).

3. I have been practicing OB/GYN for thirty-six years, with particular emphasis upon medical problems involved with premature labor and menstrual disorders. I have done extensive research in these areas, having for thirty-five years studied uterine motility as applied to premature labor and prevention of menstrual disorders.

I am familiar with the extensive scientific literature in those areas, including that concerning Lutrexin, and keep myself currently informed by the study of such literature, attendance at meetings of professional societies, and consultation with OB/GYN specialists.

I have published and collaborated in the publication of five papers on these subjects (listed in Exhibit A).

4. I have used Lutrexin in the treatment of dysmenorrhea and premature labor for approximately twenty years and have administered the drug to approximately five hundred women afflicted with these disorders. Attached hereto are reprints of two published papers (Exhibits B and C, respectively) reporting the results of administration of Lutrexin in cases of dysmenorrhea and premature labor, viz., Rezek, *The Effect of A New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea*, American Journal of Obstetrics and Gynecology, Vol. 66, No. 2, p. 396, August, 1953; Rezek, *Lutrexin in the Treatment of Premature Labor*, Annals of New York Academy of Sciences, Vol. 75, Art. 2, p. 995, January, 1959.

5. The method of investigation utilized in my study of the use of Lutrexin in premature labor (Exhibit C) plus my extensive clinical experience with the use of the drug in complications of pregnancy cannot be dismissed as of no value in showing the effectiveness of Lutrexin on the ground that my investigations are not well-controlled. Since the risk of death to the fetus in premature labor difficulties is high, the use of the double-blind, placebo type of study cannot be countenanced by any ethical or moral physician, where, as here, there exists a drug (Lutrexin) clinically-proven effective.

6. I have reviewed the report of the panel of the National Academy of Sciences-National Research Council which evaluated Lutrexin as "possibly effective" in the treatment of premature labor and dysmenorrhea, and understand that the Food and Drug Administration has subsequent to the report proposed to remove Lutrexin from the market. Further, I have studied the data of HW&D submitted to FDA in response to the proposed removal of Lutrexin from the market.

7. Based on my experience with Lutrexin, above outlined, it is my opinion that Lutrexin is effective in the treatment of premature labor and dysmenorrhea. It is established that Lutrexin is safe for these uses; I have prescribed up to 12,000 units hourly for seven days of the drug for patients suffering from

premature labor and dysmenorrheic difficulties, with no adverse side effects whatsoever.

8. Based upon my experience, discussions with OB/GYN colleagues concerning Lutrexin and upon my knowledge of the literature relating to the drug and the conditions of its uses, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as safe and effective for use in the treatment of cases of premature labor and dysmenorrhea under the conditions recommended in its labeling. Upon the same basis it is my opinion that Lutrexin has been generally recognized by OB/GYN physicians as safe for such use under such conditions for at least ten years.

9. I am prepared to testify in Court as to these matters and give supporting data to my opinions above-expressed.

(S) George H. Rezek, M.D.

GEORGE H. REZEK, M.D.

Subscribed and sworn to before me this 5th day of March, 1970.

(S) RUDOLPH GERMACK,  
*Notary Public.*

## EXHIBIT A

### CURRICULUM VITAE

DR. GEORGE HENRY REZEK

6001 Cermak Road,  
Cicero, Illinois 60650.

Year of Birth: 1905.

Medical Education: University of Illinois College of Medicine,  
Chicago, M.D. Degree in 1932.

Year of License: 1932, State of Illinois.

American Specialty Board: American Board of Obstetrics and  
Gynecology.

Primary Specialty: Obstetrics and Gynecology.

Type of Practice: Full time specialty practice.

Internship and Residence:

Research and Educational Hospital, Chicago 1932-33.

Resident in Ob/Gyn, Research and Educational Hospital  
1933-36.

Teaching Affiliation: University of Illinois, Clinical Associate  
Professor, Ob/Gyn.

Hospital Affiliation: Chairman, Department Ob/Gyn, Garfield  
Park Community Hospital.

Membership:

Chicago Gynecological Society.

Fellow American College of Surgeons.

Fellow American College of Obstetricians and Gynecolo-  
gists.

Fellow International College of Surgeons.

Professorial Appointment: University of Illinois College of  
Medicine, Chicago.

Papers Published:

Rezek, G. H.: Biologic Test for Diagnosis of Intra-uterine  
Fetal Death, AMER. JOUR. OBST. & GYNEC.,  
32:976-981, December 1936.

Rezek, G. H. and Benesohn, S. J.: Clinical and Experi-  
mental Observations on the Use of Corpus Luteum  
Extracts in Obstetrics, SURG., GYNEC. & OBST.,  
75:289-299, September 1942.

Rezek, G. H.: Effect of New Potent Uterine Relaxing  
Factor of Corpus Luteum in Treatment of Dysmenor-  
rhea, AMER. JOUR. OBST. & GYNEC., 66:396-402,  
August 1953.

Rezek, G. H.: Lutrexin in the Treatment of Premature  
Labor, ANN. N.Y. ACAD. SCI., 75:995-997, January  
9, 1959.

Rezek, G. H.: Uterine Motility and the Survival of the  
Fetus, MED. DIG., 296-297, Bombay, India, July 1963.

The undersigned hereby certifies that the above is a true  
and correct statement of his curriculum vitae

(S) George H. Rezek, M.D.

GEORGE HENRY REZEK, M. D.

Date: March 5, 1970.

WASHINGTON UNIVERSITY,  
SCHOOL OF MEDICINE,  
*St. Louis, Missouri 63110, 10 December 1969.*

DEPARTMENT OF  
OBSTETRICS AND GYNECOLOGY,  
*4911 Barnes Hospital Plaza,  
St. Louis, Missouri 63110.*  
Mr. J. H. F. DUNNING,  
*President, Hynson, Westcott and Dunning, Inc.,  
Baltimore, Maryland.*

DEAR MR. DUNNING: I certainly enjoyed seeing you again after so many years. Recalling the events of the Govt. vs. Hynson, Westcott and Dunning (?1940) took us back to our more youthful days. The issues then were much the same as the issues today: how far should the FDA go in controlling the medications available to physicians for the treatment of patients? The Judge, if you recall, said at the opening of the trial that he was sure that the Government would present evidence that the Lutein Tablets were ineffectual and that Hynson, Westcott and Dunning would present evidence that the medication was efficacious.

The situation regarding Lutrexin today is not quite the same. Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women.

The NRC panel considered Lutrexin as possibly effective. This opinion of the panel does not mean that Lutrexin may possibly contain an active component. It means, on the contrary, that Lutrexin may be possibly effective in the conditions for which it is recommended, i.e., dysmenorrhea, threatened abortion or premature labor. The situation today is much the same, however, as 30 years ago in that the FDA seems to be interpreting 'possibly effective' as ineffective and, once more, the clinical evidence becomes of paramount importance.

The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective. Lutrexin is recommended, for example, in premature labor. Uterine contractility is essential for delivery of the child but when uterine contractility comes prematurely the child may be lost from prematurity. Women have been forced to face the tragedy of premature labor for centuries because medical science has not provided as yet a complete explanation for premature labor, nor has medical science provided a scientifically rational method for preventing premature labor, or for stopping premature labor once it has started. A great deal is known, of course, concerning the effects of both estrogen and progesterone on the uterine muscle of both animals and man, but this information has not resulted in any truly rational method of treating premature labor. Lutrexin, since it contains an active principle which relaxes the uterus, should be available for the treatment of premature labor and should continue to be available until such time as a fully rational and effective treatment has been discovered.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multivitamins.

The problem resolves itself into two direct questions:

1. Does the FDA have the right to exclude a harmless remedy which may be "possibly effective"?
2. Should the FDA exclude a harmless remedy with biological potency just because the NRC panel noted, in its wisdom, that the product was "possibly effective"?

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

Sincerely yours,

WILLARD M. ALLEN, M.D.,  
*Professor and Chairman,  
 Department of Obstetrics and Gynecology.*

WMA:en

15 June 1970.

I hereby certify that the above is a Xerox copy of a letter which I mailed to Mr. Dunning on Dec. 10, 1969. I also certify that this letter was written by myself.

WILLARD M. ALLEN, M.D.  
 (S) Willard M. Allen, M.D.  
*State of Missouri, City of St. Louis.*

Subscribed and sworn before me this 15th day of June, 1970.

(S) PATRICIA K. TILLEY,  
*Notary Public.*

#### PROFESSIONAL STATISTICS

ALLEN, Dr. WILLARD M., Professor and Chairman, Department of Obstetrics and Gynecology, Washington University School of Medicine.

Year of Birth: 1904.

Medical Education: M.D., 1932 University of Rochester School of Medicine and Dentistry.

Year of License: 1940.

American Specialty Board: American Board of Obstetrics and Gynecology.

Primary Speciality: Obstetrics and Gynecology.

Societies:

American Association of Obstetrics and Gynecologists.

American Gynecological Society.

American College of Obstetricians and Gynecologists.

American College of Surgeons.

The Endocrine Society.

American Radium Society.  
American Medical Association.

**Miscellaneous:**

Professor and Chairman, Department of Obstetrics and Gynecology, Washington School of Medicine, 1940—  
Member of Panel on Drugs Used in Disturbances of the Reproductive System of the National Academy of Sciences-National Research Council.

*Affidavit of Sylvester W. Trythall, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment*

STATE OF MICHIGAN,  
County of Wayne, ss:

Sylvester W. Trythall, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's Memorandum in Opposition to Defendants' Motion to Dismiss and in the Alternative for Summary Judgment, filed herewith in the above captioned cause.

2. I received an M.D. degree from University of Michigan School of Medicine in 1932, and was licensed to practice medicine in Michigan in 1932. My primary specialty is obstetrics and gynecology and I am certified by the American Board of Obstetrics and Gynecology, and am a fellow of the American College of Obstetricians and Gynecologists, as well as the American College of Surgeons, the American College of Obstetricians and Gynecologists, American Infertility Society and the International Infertility Society. I am affiliated with Crittenden General Hospital in Detroit, Michigan. My academic and administrative posts have been as follows:

Senior Attending Gynecologist  
Chief of OB/GYN

3. I have engaged in the active practice of obstetrics and gynecology for approximately 37 years, and estimate that I have delivered or been associated in the delivery of over 10,000 babies. For the past 25 years I have been particularly practicing in the area of infertility and premature labor and threatened



and habitual abortion. I have used Lutrexin in the treatment of cases of threatened and habitual abortion, and premature labor for more than 15 years. During that time I have administered Lutrexin to a large number of women to prevent premature delivery of the infant. I have done a number of well-controlled studies in this area and a number of my published studies is attached hereto, made a part hereof and marked "Schedule A". In all of these studies I used Lutrexin as mentioned therein, and have found it to be a safe and effective drug.

4. From my extensive training and experience with clinical investigators and clinical investigations of drug and disease situations, as well as my own clinical studies, I am of the opinion that—

a) There are case situations in which double-blind or any type of placebo methods of clinical investigation may be unethical, immoral and even illegal;

b) cases involving threatened and habitual abortion and premature labor are such types of case situations;

c) in such cases, studies made by competent clinical investigators based on statistics, and historical control (including patient's own history) would be expected to produce "well controlled" results under the circumstances.

5. I am advised that the report of the panel of the National Academy of Sciences-National Research Council found Lutrexin to be "possibly effective" in the treatment of threatened abortion and premature labor, and understand that the Food and Drug Administration has moved to take Lutrexin off the market based upon this "possibly effective" evaluation, which the FDA has, without proper scientific evidence, expanded into an "ineffective" situation. In addition, I have reviewed the data of Hynson, Westcott and Dunning prepared by Drs. Gratton, Rezek, Majewski and Gray.

6. It is my opinion, based upon my experience with Lutrexin, indicated above, that Lutrexin is effective in the treatment of cases of threatened abortion and premature labor. I have found, in my practice, that it (together with cervical suture in some instances) is the most effective therapeutic agent for these indications. I have now under my care five selected pregnant women with a history of premature labor and one or more abortions due thereto. I have all of these women on regular doses of Lutrexin and furthermore, I do not believe I

could successfully practice in the aforementioned area of therapeutics if I did not have Lutrexin available. The safety of Lutrexin, not only in the dosage suggested in the drug's labeling but in amounts substantially in excess thereof, is beyond dispute; and I have never encountered any adverse effects in either mother or infant. Removal of Lutrexin from the OB/GYN's armamentarium would in my opinion border on the reprehensible, for, it would leave a currently unfillable void therein.

7. I am advised that Dr. Willard M. Allen, Professor and Chairman of the Department of Obstetrics and Gynecology in the School of Medicine of Washington University in St. Louis, Missouri, was a member of the N. R. C. panel which found Lutrexin "possibly effective". I consider Dr. Allen to be one of the foremost experts in OB/GYN in the country today.

8. I have also examined a letter of Dr. Allen's which, I am advised, has been filed with the Commissioner, Charles Edwards, M. D. of the Food & Drug Administration (Department of H. E. W.), and after appropriate oaths and acknowledgment by a Notary Public has been filed with the Clerk of the Court in this cause. In this letter and affidavit Dr. Allen states, among other things, as follows:

Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women. The NRC panel considered Lutrexin as possibly effective. This opinion of the panel does not mean that Lutrexin may possibly contain an active component. It means, on the contrary, that Lutrexin may be possibly effective in the conditions for which it is recommended, i.e., dysmenorrhea, threatened abortion or premature labor. The situation today is much the same, however, as 30 years ago in that the FDA seems to be interpreting "possibly effective" as ineffective and, once more, clinical evidence becomes of paramount importance.

The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to

the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective. Lutrexin is recommended, for example, in premature labor. Uterine contractility is essential for delivery of the child but when uterine contractility comes prematurely the child may be lost from prematurity. Women have been forced to face the tragedy of premature labor for centuries because medical science has not provided as yet a complete explanation for premature labor, nor has medical science provided a scientifically rational method for preventing premature labor, or for stopping premature labor once it has started \* \* \*.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multi-vitamins \* \* \*.

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

I wholeheartedly agree with Dr. Allen's statements concerning Lutrexin.

9. Based upon my experience, communications with OB/GYN practitioners in Detroit, Michigan and elsewhere, and upon my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as both safe and effective in treatment of threatened abortion and premature labor. At the present time I have four patients on Lutrexin routine for RX of habitual late abortion.

10. I am prepared to testify as to these matters, and to present data to support the opinions expressed above, in a proceeding in court or before the Food and Drug Administration.

(S) S. W. Trythall, M.D.

SYLVESTER W. TRYTHALL.

Subscribed and sworn to before me this 14th day of September, 1970.

(S) ROSEMARY SCOTT,

*Notary Public, Wayne County, Michigan.*

## PROFESSIONAL STATISTICS

AMA X

DO \_\_\_\_\_

ADA \_\_\_\_\_

AVMA \_\_\_\_\_

DR. SYLVESTER W. TRYTHALL, 20905 Green Field Road, Southfield, Michigan 48075.

Year of Birth: 1903.

Medical Education: University of Michigan Medical School, Ann Arbor M.D. Degree in 1932.

Year of License: 1935.

American Specialty Board: American Board of Obstetrics and Gynecology.

Primary Specialty: Obstetrics and Gynecology.

Type of Practice: Full time general practice or Other full time specialty practice.

Special Societies:

American College of Surgeons.

American College of Obstetricians and Gynecologists.

Date: June 14, 1968.

*Affidavit of Fred B. Gray, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendant's Motion To Dismiss and in the Alternative for Summary Judgment*

STATE OF MICHIGAN,  
County of Kent, ss:

Fred B. Gray, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in Opposition to Defendants' Motion to Dismiss and in the Alternative for Summary Judgment, filed herewith in the above captioned cause.

2. I received an M. D. degree from Vanderbilt University School of Medicine in 1940, and was licensed to practice medicine in Michigan in 1945. My primary specialty is obstetrics and gynecology and I am certified by the American Board of Obstetrics and Gynecology, and am a fellow of the American College of Obstetricians and Gynecologists, as well as the American College of Surgeons and the American College of

Obstetricians and Gynecologists. I am affiliated with both Butterworth and Blodgett Hospitals in Grand Rapids, Michigan.

3. I have engaged in the active practice of obstetrics and gynecology for approximately 25 years, and estimate that I have delivered approximately 7,000 babies. I have used Lutrexin in the treatment of cases of threatened and habitual abortion and premature labor for more than 12 years. During that time I have administered Lutrexin to a large number of women to prevent premature delivery of the infant, and have made what I believe to be a well-controlled study of 15 selected cases, a copy of which study is attached hereto, made a part hereof and marked Exhibit 1.

4. From my extensive training and experience with clinical investigators and clinical investigations of drug and disease situations, I am of the opinion that—

a) there are case situations in which double-blind or any type of placebo methods of clinical investigation may be unethical, immoral and even illegal;

b) cases involving threatened and habitual abortion and premature labor may well be such types of case situations;

c) in such cases studies made by competent clinical investigators based on statistics, or historical control (including patient's own history) may well be expected to produce "well controlled" results under the circumstances.

5. I am advised that the report of the panel of the National Academy of Sciences-National Research Council found Lutrexin to be "possibly effective" in the treatment of threatened abortion and premature labor, and understand that the Food and Drug Administration has moved to take Lutrexin off the market based upon this "possibly effective" evaluation. In addition, I have reviewed the data of Hynson, Westcott and Dunning submitted to FDA in response to the panel's report.

6. It is my opinion, based upon my experience with Lutrexin, indicated above, that Lutrexin is effective in the treatment of cases of threatened abortion and premature labor. I have found, in my practice, that it is the most effective therapeutic agent for these indications. The safety of Lutrexin, not only in the dosage suggested in the drug's labeling but in amounts substantially in excess thereof, is beyond dispute; and I have never

encountered any adverse effects in either mother or infant. Removal of Lutrexin from the OB/GYN's armamentarium would in my opinion border on the reprehensible, for, it would leave a currently unfillable void therein.

7. I am advised that Dr. Willard M. Allen, Professor and Chairman of the Department of Obstetrics and Gynecology in the School of Medicine of Washington University in St. Louis, Missouri, was a member of the N. R. C. panel which found Lutrexin "possibly effective". I consider Dr. Allen to be one of the foremost experts in OB/GYN in the country today.

8. I have also examined a letter of Dr. Allen's which, I am advised, has been filed with the Commissioner, Charles Edwards, M. D. of the Food & Drug Administration (Department of H. E. W.). In this letter Dr. Allen states, among other things, as follows:

Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women. The NRC panel considered Lutrexin as possibly effective. This opinion of the panel does not mean that Lutrexin may possibly contain an active component. It means, on the contrary, that Lutrexin may be possibly effective in the conditions for which it is recommended, i.e., dysmenorrhea, threatened abortion or premature labor. The situation today is much the same, however, as 30 years ago in that the FDA seems to be interpreting "possibly effective" as ineffective and, once more, clinical evidence becomes of paramount importance.

The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective. Lutrexin is recommended, for example, in premature labor. Uterine contractility is essential for delivery of the child but when uterine contractility comes prematurely the child may be lost from prematurity. Women have been forced to face the tragedy of premature labor for centuries

because medical science has not provided as yet a complete explanation for premature labor, nor has medical science provided a scientifically rational method for preventing premature labor, or for stopping premature labor once it has started \* \* \*.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multivitamins \* \* \*.

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

I wholeheartedly agree with Dr. Allen's statements concerning Lutrexin.

9. Based upon my experience, communications with OB/GYN practitioners in Grand Rapids, Michigan and elsewhere, and upon my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as both safe and effective in treatment of threatened abortion and premature labor.

10. I am prepared to testify as to these matters, and to present data to support the opinions expressed above, in a proceeding in court or before the Food and Drug Administration.

(S) Fred B. Gray, M.D.

FRED B. GRAY, M.D.

Subscribed and sworn to before me this 6th day of March, 1970.

(S) GORDON J. DUPREY,  
Notary Public, Kent County, Michigan,  
My Commission Expires: Feb. 6, 1973.

AMA Directory—AM Directory OB/GYN

#### PROFESSIONAL STATISTICS

DR. FRED B. GRAY,  
456 Cherry Street, S.E.,  
Grand Rapids, Michigan 49503.

Year of Birth: 1912.

Medical Education: Vanderbilt University School of Medicine,  
Nashville, Tennessee, M.D. Degree in 1940.



Year of License: 1945.

Amer. Specialty Board: American Board of Obstetrics and Gynecology.

Primary Specialty: Obstetrics and Gynecology.

Type of Practice: Full time specialty practice.

Internship and Residence:

Butterworth Hospital, July 1940-41.

Vanderbilt Hospital, 1941-42.

Butterworth Hospital, 1945-47.

Hospital Affiliation:

Butterworth Hospital, Senior.

Blodgett Hospital (Visiting).

Membership:

Fellow American College of Surg.

KCMS.

American Medical Association.

American College of Obstetricians and Gynecologists.

November 1968.

*Affidavit of Joseph F. Sadusk, Jr., M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment*

STATE OF MICHIGAN,

County of Wayne, ss:

Joseph F. Sadusk, Jr., being duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's Memorandum in Opposition to Defendant's Motion to Dismiss and in the Alternative for Summary Judgment, filed herewith in in the above-captioned cause.

2. I am a physician, currently Vice President for Medical and Scientific Affairs of Parke, Davis & Company, manufacturer of pharmaceuticals and allied products; formerly Professor of Medicine and Associate Dean of the School of Medicine of Johns Hopkins University; formerly Director of the Bureau of Medicine and Medical Director, Food & Drug Administra-



tion, U.S. Department of Health, Education and Welfare; and a more detailed curriculum vita and List of Publications are attached hereto, made a part hereof and marked Exhibits A and B.

3. That I made a speech on October 8, 1964 to the American College of Physicians which was presented in the Bulletin of the American College of Physicians in the November-December 1964 issue, at which time I was Director of the Bureau of Medicine and Medical Director of the FDA. (A true copy of which is attached hereto and made a part hereof, and marked Exhibit C). Said speech was approved by the Office of the Commissioner, FDA, and may be said to be in accord with FDA policies.

4. That I am still of the same opinion expressed therein concerning "well controlled" clinical studies.

5. From my extensive training and experience in clinical investigations of drug and disease situations I am of the opinion that—

a) there are case situations in which double-blind or any type of placebo methods of clinical investigation may be unethical, immoral and even illegal;

b) cases involving threatened and habitual abortions and premature labor may well be such types of case situations;

c) in such cases studies made by competent clinical investigators based on statistics, or historical controls (including patient's own history) may well be expected to produce "well controlled" results under the circumstances.

6. That I am prepared to testify in open court as to the foregoing matters.

(S) Joseph F. Sadusk, Jr.  
JOSEPH F. SADUSK, Jr.,

Subscribed and sworn to before me, a Notary Public in and for the County of Wayne and State of Michigan, on this 22nd day of January, 1970.

(S) RINA J. BABUSCI,  
Notary Public,  
Wayne County, Michigan,  
My Commission Expires: 10-26-73.

[Exhibit A]

## CURRICULUM VITAE

JOSEPH FRANCIS SADUSK, JR., A.B., MD.

*Vice President, Medical and Scientific Affairs,  
Parke, Davis & Company.*

Born October 4, 1909, Baltimore, Maryland.

Degrees and Fellowships:

1927-29—Loyola College (Baltimore).

1929-31—A.B., Johns Hopkins University.

1931-35—M.D., Johns Hopkins University.

1933-35—Henry Strong Denison Fellow in Physiological  
Chemistry.

House Officership Training:

1935-36—Resident House Officer in Medicine, Johns Hop-  
kins Hospital.

1936-37—Resident House Officer in Obstetrics, Johns  
Hopkins Hospital.

1937-38—Asst. Resident in Medicine, New Haven Hos-  
pital.

1938-39—Asst. Resident in Obstetrics, Johns Hopkins Hos-  
pital.

1939-40—Resident in Medicine, New Haven Hospital.

Faculty Positions:

1937-38—Assistant in Medicine, Yale Univ. Medical  
School.

1938-42—Instructor in Medicine, Yale Univ. Medical  
School.

1946-47—Asst. Professor of Medicine, Yale Univ. Medical  
School.

1947-48—Clinical Instructor in Medicine, New York Uni-  
versity College of Medicine.

1948-49—Adjunct Clinical Professor of Medicine, George  
Washington University School of Medicine.

1949-58—Asst. Clinical Professor of Medicine, Stanford  
Medical School.

1958-62—Assoc. Clinical Professor of Medicine, Stanford  
Medical School.

1962-64—Professor and Chairman, Department of Pre-  
ventive Medicine and Community Health, George  
Washington University School of Medicine.

1962-64—Director of University Clinics, George Washington University Hospital.

1962-66—Professor of Preventive Medicine and Community Health, George Washington University.

1966-67—Professor of Medicine, Johns Hopkins University.

1966-67—Associate Dean for Community Medicine, The Johns Hopkins University School of Medicine.

1967— —Adjunct Professor of Medicine, Wayne State University School of Medicine.

#### Hospital Appointments:

1940-42 and 1946-47—Associate Visiting Physician, New Haven Hospital.

1947-48—Assistant Visiting Physician, Bellevue Hospital (New York).

1948-49—Associate Visiting Physician, George Washington University and Gallinger Hospitals (Washington, D.C.)

1949-62—Visiting Physician, Stanford-Lane Hospital and Stanford University Hospital (San Francisco-Palo Alto)

1959-62—Staff Physician, Presbyterian Medical Center (San Francisco)

1949-62—Staff Physician, Peralta, Providence and Merritt Hospitals (Oakland)

1958-59—President, Peralta Hospital Medical Staff

1957-62—Member, Board of Trustees, Peralta Hospital

1957-62—Member, Medical Advisory Board, Peralta Hospital

1962-66—Staff Physician, George Washington University Hospital

1963-66—Consultant in Infectious Disease, District of Columbia Children's Hospital

1963-66—Consulting Staff, Washington Hospital Center

1966-67—Physician, Johns Hopkins Hospital

1967— —Senior Associate Attending Physician, Detroit General Hospital

#### Consultants Positions:

1941-42—Consultant to Secretary of War.

1941-42—Member, Commission on Pneumonia, U.S. Army Epidemiological Board.

1946-47—Consultant to Secretary of War.

- 1946-47—Member, Commission on Viral and Rickettsial Diseases, U.S. Army Epidemiological Board.
- 1946-48—Consultant in Tropical Medicine to U.S. Army Research and Post Graduate School.
- 1946-47—Consultant in Internal Medicine, Laurel Heights Sanitarium, Shelton, Connecticut.
- 1949-52—Consultant to Secretary of Defense.
- 1949-52—Consultant in Infectious Diseases, Oakland, VA Hospital.
- 1955-61—Area Consultant to Veterans Administration in Tropical Medicine.
- 1955-61—Consultant in Tropical Medicine, San Francisco, V.A. Hospital.
- 1958-62—Chairman, Medical Advisory Committee, Oakland V.A. Hospital.
- 1961-64—Member, Civilian Health and Medical Advisory Council (Asst. Secretary of Defense for Manpower).
- 1962-64—Executive Reserve (Secretary of Defense—United States Government.

#### Government Positions:

U.S. Army—1942-46—Captain to Colonel, Medical Corps—

1. Faculty, Army Medical School (Dept. Bacteriology and School of Tropical Medicine)—1942.
2. Staff, Hawaiian Department (Spec. Assignment by Secretary of War)—1942-43.
3. Executive Officer, Special Mission on Scrub Typhus, U.S. Army—1943.
4. United States of America Typhus Commission—Executive Officer—1943-46.

#### Department of Defense—

Executive Director, Committee on Medical Sciences, Research and Development Board, Secretary of Defense—1948-49.

#### Department of Health, Education and Welfare

Medical Director, Food and Drug Administration—1964-66.

#### Other Administrative:

1947-48—Associate Medical Director, Prudential Insurance Company.

1967-68—Vice President, Medical Affairs; Parke, Davis & Company.

1968-Present—Vice President, Medical and Scientific Affairs; Parke, Davis & Company.

1968-Present—Member of the Board of Directors; Parke, Davis & Company.

1969—Member, Board of Trustees, St. Johns Hospital, Detroit, and Chairman of Planning Committee.

1969—Member, Board of Trustees, Lindenwood College II.

#### Awards and Decorations:

Legion of Merit and Oak Leaf Cluster—1943 and 1954.

U.S.A. Typhus Commission Medical—1964.

Fourth Annual Roland T. Lakey Lecture Award, The Rho Chi Pharmaceutical Honor Society, Wayne State University College Pharmacy—1967.

Honorary Member, American Medical Society of Vienna (Austria)—1969.

#### Medical Society Committee Appointments:

1950-55—Chairman, Committee on Medical Practice, Alameda-Contra Costa County Medical Association.

1954-58—Chairman, Medical Review and Advisory Board, California Medical Association.

1956-66—Member, and Chairman (1962-66), Committee on Medicolegal Problems, American Medical Association.

1957-59—Chairman, American Medical Association-American Hospital Association Committee on Medicolegal Education.

1960-69—Member, American Medical Association Liaison Committee with American Bar Association.

1958-66—Member, Committee on Insurance, American College of Physicians.

1960-66—Member, Board of Trustees, American College of Physicians Group Life Insurance Plan.

1950-62—Various other Committees of Alameda-Contra Costa Medical Association.

1963-65—Member, Committee on Medicolegal Education, Medical Society of the District of Columbia; Consultant—1965-66.

1967-68—Member, Committee on Social Policy for Medical Care, New York Academy of Medicine.

1967—President—Pharmaceutical Manufacturers Association Foundation Advisory Committee on the Faculty Development Awards.

1967-Present—Committee on Medicine and Pediatrics (The Society of Medical Consultants to the Armed Forces).

#### Medical Society Membership:

Fellow of American College of Physicians.

American Society for Clinical Investigation.

American Federation for Clinical Research.

American Society of Tropical Medicine.

American Medical Association and other state and county Medical Societies (Connecticut, New Jersey, California, Maryland, Michigan and District of Columbia).

American Society of Internal Medicine.

California Society of Internal Medicine (President 1961-62); Honorary Life Member (1962-Present).

Tropical Medicine Association of Washington, D.C.

Academy of Medicine of Washington, D.C.

Society of Medical Consultants to the Armed Forces.

Michigan Society of Internal Medicine.

American Public Health Association.

American Society of Tropical Medicine and Hygiene.

American Therapeutic Society.

#### Internal Medicine:

1944—Certified by American Board of Internal Medicine.

1949-62—Practice of Internal Medicine, Oakland, California.

States Licer sed to Practice: California, Connecticut, District of Columbia, Maryland, Michigan, New Jersey, New York.

#### Clubs:

The 100 Club (Oakland, 1953-64) (President 1960-61).

Cosmos Club (Washington, D.C.), 1962-President.

The Hundred Club of Detroit, 1967-

The Detroit Club, 1967-

Detroit Athletic Club, 1967-

Grosse Pointe Club, 1968-

**Publications:**

Publications in medical journals and contributor to medical textbooks in the field of biochemistry, infectious diseases, chemotherapy, anti-syphilitic therapy, viral and rickettsial diseases, medicolegal problems, regulation of drugs, and biomedical science communications.

[Exhibit C]

(Vol. 5, No. 6 November-December, 1964)

**THE BULLETIN OF THE AMERICAN COLLEGE OF PHYSICIANS**

**THE DEFINITION OF THE EFFICACY OF A DRUG UNDER THE LAW**

JOSEPH F. SADUSK, JR., F.A.C.P., Medical Director, Food and Drug Administration, U. S. Department of Health, Education, and Welfare.

In 1912, an amendment to the Food and Drug Act of 1906 established the first Federal authority to act against drugs that were labeled with false and fraudulent claims for therapeutic effectiveness. However, such false claims made "out of ignorance" could not be attacked under this amendment, in other words, the burden of proof was on the Government to prove fraud on the part of the manufacturer.

The Elixir of Sulfanilamide disaster led to the new drug provisions of the Federal Food, Drug, and Cosmetic Act of 1938. While basic provisions in this Act required a manufacturer to establish safety of a drug before it could be marketed, the Food and Drug Administration had to permit the marketing of such a new drug when an application showed it to be safe, even though evidence of effectiveness was lacking. Nevertheless, the Food and Drug Administration did have limited authority under these 1938 provisions to deal with effectiveness through its power to rule in safety, since many drugs are capable of causing serious adverse effects; and it was a common sense conclusion that a safety decision could be reached only on the basis that the potential benefits of a drug outweighed the risk involved in its use.

Presented in a Symposium on Drug Investigation and Therapy, at the Second Fall Meeting of the American College of Physicians, Los Angeles, California, October 8, 1964.



The Kefauver-Harris Amendments of 1962 revised the definition of a new drug to say that a new drug is one which by reason of its composition is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." As a result of these amendments, a new drug application can now be rejected not only when there is insufficient evidence to establish its safety, but also if there is a lack of substantial evidence to show that the drug will have the effect it purports or is represented to have under conditions of use recommended in the proposed labeling.

Let us define several terms. The word *labeling* includes the contents of the package circular which the manufacturer is required to enclose with the bottle of medication. This circular may vary from several hundred to a thousand or more words and briefly, but very specifically, presents the trade name, generic name, chemistry, pharmacology, clinical indications, precautions, side effects, contraindications, routes, methods, and dosage. Much effort is expended by the manufacturer and the Food and Drug Administration on this labeling which represents a full summary of knowledge of chemists, pharmacologists, investigators, and clinicians. Under the present conditions of distribution of this package circular, it does not get to the physician as effectively as we should like; though it is generally true that with a very modest effort the physician may obtain it from his pharmacist or examine it from a physician's sample package that comes to his desk. In addition, not only does the 1962 Amendment require the drug manufacturer to furnish a copy of the Food and Drug Administration approved package circular for a new drug to the physician upon request, but all other promotional material for drugs, including advertisements, are required to contain summaries drawn from the package brochure. Nevertheless, the Food and Drug Administration is giving serious consideration to better methods of distribution of present package insert information to physicians and other practitioners, hospitals, and pharmacists.

As used in the law, the term "*substantial evidence*" is defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts



qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use" as recommended in the proposed labeling.

Let us inquire into this definition of efficacy as expressed in the law. We need to discuss further and in such detail as time permits the following phrases:

1. Adequate and Well-Controlled Investigations.
2. Experts Qualified by Scientific Training and Experience.
3. On the Basis of Which It Can Fairly and Responsibly be Concluded That the Drug Will Have Its Claimed Effect.

The three parts of this definition arose out of the Congress' belief, based on the Kefauver investigations, that too many drugs were being promoted on the strength of random observations by physicians of no special competence in drug investigation, thus producing a type of evidence of essentially the testimonial or other poorly controlled character. No really responsible group of medical experts could accept this sort of evidence as a basis for approval of medical claims.

In final analysis, what was intended here was to require the development of the kind of scientific evidence that would enable an expert group, such as consultants selected by the Council on Drugs of the American Medical Association to review a particular drug, to come to a conclusion that the drug could reasonably be expected to perform in the clinical practice for which it was intended in the way that the labeling said it would.

Let us take the three parts one by one.

### 1. Adequate and Well-Controlled Investigations

Obviously, many experimental factors must be controlled and, in general, the effect on the disease process in patients receiving the drug needs to be compared with patients with similar disease conditions who do not receive the drug. This is preferably done by placebo comparisons in well-designed double-blind clinical studies.

But this is not the only type of study that can be called well-controlled. Sometimes such studies are not ethically permissible or, for practical reasons, are not feasible. Here the design of the study, the competence and experience of the investigator, and the adequacy of the observations and laboratory and other test procedures that are employed to record and weigh the clinical effects of the drug take on paramount importance. With some drugs intended for use in disease states, the natural histories of which are reasonably well understood and in which the pharmacological behavior of the drug can be observed by objective measurements, the blind and double-blind studies take on less significance. And even in states where there are little or no objective measures of patient response, careful planning coupled with systematic observation and accurate recording of the patient's course may qualify as a well-controlled study. The use of other disciplines such as statistics may provide the extra support to make the study an acceptable and convincing one.

## 2. Experts Qualified by Scientific Training and Experience

And now let us address ourselves to a discussion of the part of the law which defines an expert investigator—"experts qualified by scientific training and experience." Here we are faced with the need of determining the quality of the investigator who furnishes the evidence upon which the efficacy and safety of a drug is determined. Since the scientific community has not specifically defined or described those criteria which establish the competency of an investigator, it does not seem likely that a Governmental agency will ever be able to establish such standards. It is clear that the Food and Drug Administration will have to approach this task as any scientific administrator does—to consider each investigator on the merits of his curriculum vitae, his past record of accomplishment, the scientific environment in which he is doing the investigation, and the nature and quality of the recorded observations. Certainly, it does not seem likely that the Food and Drug Administration will ever publish a list of so-called "qualified" investigators.

We have heard stated that only physicians in the course of their practice can determine the effectiveness of drugs and what

drug to employ in a particular patient. The law does not interfere with these ideas insofar as the use of a drug is concerned for that doctor's patient, but it does prevent the marketing of a new drug with labeling and advertising making unsupported therapeutic claims.

It is common knowledge that the pharmaceutical industry is faced with a significant issue in the shortage of qualified investigators. Drugs are becoming more and more complex and the use of the general doctor, without specific experience in clinical investigation, in testing drugs in his office in the midst of a busy practice is probably coming to an end. The need for training of physicians in the drug research field has reached a critical stage, and this problem must be met by the joint efforts of government, industry, and the scientific community.

### 3. On the Basis of Which It Can Fairly and Responsibly be Concluded That the Drug Will Have Its Claimed Effect

The third and most important part of the definition of "substantial evidence" requires that it provide a basis on which a properly qualified expert can fairly and responsibly conclude that the drug will have effectiveness claimed for it.

Neither legally nor medically is there any requirement that all investigators show effectiveness of the drug being studied. Nor is there a requirement that any fixed number of investigations be made, or a fixed number of investigators used, or indeed that the drug under study be found more effective than other drugs for the same purpose.

Since medical investigation cannot always be an exact science the law does not require that the evidence demonstrate effectiveness beyond peradventure.

What is required is a body of scientific data drawn from the investigations that will be convincing to those responsible for the decision to approve or not to approve the marketing of the drug. It must be assumed that these responsible officials have the qualifications to make an evaluation of the data. If they do not, they must draw upon the scientific community for the resource people who do. Here we expect to obtain assistance from our Advisory Committees and Panels which presently are in the planning state in the Bureau of Medicine. Here we expect

to bring in a substantial number of consultants from the scientific community to advise us on decisions and to prepare guidelines for review.

But no panel and no consultant can help us unless provided with the kind of data that they are entitled to expect as a foundation for *responsible* decision. We cannot ask these experts to act on testimonials or random observations. We will not act on them ourselves.

What we want, and what the law requires, is data that would enable the appropriately qualified experts to say responsibly whether or not the drug may be expected to perform as it is represented. This kind of evidence is not hard for the qualified person to recognize when he sees it.

You are doubtless aware of the difference of opinion which exists between the Food and Drug Administration and Industry as to the requirements for efficacy testing of drugs manufactured and approved prior to 1962. The Food and Drug Administration holds that the effectiveness provisions of the Kefauver-Harris Amendments apply not only to the approval of new drug applications received after enactment of the 1962 Amendments, but that after October 9, 1964 these provisions will also apply to all drugs for which new drug applications were cleared since 1938. However, the Pharmaceutical Manufacturers Association and a number of its member firms have filed suit in the Federal Court at Wilmington, Delaware in an effort to establish that the Food and Drug Administration does not have authority to require reports for drugs cleared through the new drug procedures in previous years, but which the industry now regards as "no longer new drugs."

The results of that litigation may have a very important bearing on whether the Food and Drug Administration may apply these new effectiveness provisions to many drugs now on the market. At issue is the question of whether the drug manufacturer must offer substantial evidence that the drug he is marketing is effective for the purposes claimed in its labeling; or whether he is entitled to continue to market it unless the Food and Drug Administration develops adequate evidence to assume the burden of proof in court that the drug is ineffective for the purposes claimed. This issue is of major concern to the medical profession as well as to the public generally and drug

manufacturers. The outcome will be of critical importance in determining whether the Food and Drug Administration can assure the effectiveness of the Nation's drug supply.

Whether or not the issue is to be resolved in favor of the Food and Drug Administration, the task of reevaluating the effectiveness of drugs now on the market must be accomplished. On the one hand it would be on the basis of these new provisions of the law; on the other hand it would be under the old law requiring case by case litigation in the courts. In either event, years of effort may be required even with the fullest cooperation of the medical community and the pharmaceutical industry.

Realizing the long and difficult task ahead for the Bureau of Medicine, the Commissioner presented a list of certain categories of drugs to the Subcommittee on Reorganization and Internal Organization of the Senate Committee on Government Operations on May 28, 1964, for priority review. He has very recently accepted from the Bureau of Medicine a list of these thirteen categories of drugs in order of priority for the Bureau to apply its initial review efforts:

1. Proteolytic enzymes (oral and injectable).
2. Progestational agents.
3. Drugs offered for anxiety and apprehensive states, most tranquilizers, monoamine oxidase inhibitors.
4. Non-prescription iron preparations.
5. Pediatric dosages.
6. Topical ophthalmic antibiotic combinations.
7. A number of sustained-release drugs.
8. Other topical antibiotic combination products.
9. Bioflavonoids.
10. Hormone creams.
11. Drugs used in pregnancy.
12. Topical antihistamines.
13. Topical 'caines (local anesthetics).

It must be realized that this order of priority may change with time and indeed certain specific drugs, or even categories of drugs, may be deemed in the future to be of higher priority than those listed.

In closing, we trust you realize that the law now provides an instrumentality for the Scientific Community, the Pharmaceu-

tical Industry, and the Food and Drug Administration to join and coordinate their efforts to reasonably assure our Nation that everything possible has been done in the light of scientific knowledge to promote the safety, effectiveness, and reliability of the country's drug supply.

36 FR. 11763 (June 18, 1971)

FOOD AND DRUG ADMINISTRATION

HYNISON, WESTCOTT & DUNNING, INC.

*Notice of Withdrawal of Approval of New-Drug Applications*

On March 22, 1969, there was published in the **FEDERAL REGISTER** (34 FR. 5556) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications for drugs containing lututrin on the ground that there is a lack of substantial evidence that lututrin has the effect or contributes to the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Hynson, Westcott & Dunning, Inc. Charles and Chase Streets, Baltimore, Mr. 21201, holder of NDA No. 8-986, Lutrexin tablets and NDA No. 10-144, Trexonest tablets by the October 16, 1970 letter of its counsel, has requested a hearing on the following issues:

- (1) Whether its lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355 under section 107 (c) of Public Law 87-781; (2) whether its lututrin drugs are "new drugs" within the meaning of 21 U.S.C. 321(p) (1); and (3) whether there is a lack of substantial evidence of effectiveness to support the claims made for Lutrexin.

In support of its request for a hearing on the issue of substantial evidence of effectiveness, Hynson, Westcott, and Dunning, Inc. (hereinafter referred to as "HW&D") has submitted a list of its medical documentation previously filed with the Agency, including all data submitted in connection with NDA No. 10-



144, correspondence between HW&D officials and the Agency or other persons, labeling for the lututrin drugs, literature articles submitted to the National Academy of Science-National Research Council, and the HW&D letter of August 18, 1969, in which the company first elected to avail itself of the opportunity for hearing.

To support its hearing request on the contentions that HW&D's lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355, the company has submitted copies of its pleadings, legal memorandum, exhibits, and affidavits, as well as the transcript and order in *Hynson, Westcott and Dunning, Inc. v. Finch* (C.A. No. 211112, D. Md., decided Sept. 11, 1970).

The Commissioner of Food and Drugs has reviewed HW&D's request for hearing and the medical documentation submitted, and makes the following findings:

### *1. The drugs, their rationale and claims*

a. Lutrexin is labeled as containing 3,000 units of lututrin per tablet. Lututrin is claimed to be a pig uterine relaxing hormone effective in the treatment of functional dysmenorrhea, selected cases of premature labor and threatened and habitual abortion. The package insert claims the drug has demonstrated activity on the living animal uterus, that it relaxes the contracted uterine muscle by direct action thereon, or by blocking pituitary action.

b. Treximest is labeled as containing 500 units of lututrin and 1.0 milligrams of estrogen, in the form of sodium estrone sulfate, per tablet. Treximest is recommended for the treatment of menopausal disorders. The package insert claims that the combination is more effective than lututrin or estrogen alone and points to lututrin as the responsible agent in the drug's effectiveness.

### *II. The applicable regulations*

HW&D's contention that it has an unconditional right to a hearing is denied. The hearing regulations, 21 CFR 130.14, require that a person seeking a hearing set forth specific facts showing the existence of genuine and substantial fact issues which requires a hearing. The order of May 8, 1970 (35 F.R.

7250) granted persons involved in notices of hearing, including HW&D, 30 days in which to amend their requests for hearing to comply with the new regulations. The company was given actual notice on May 19, 1970, that it was required to comply with these regulations in order to properly avail itself of an opportunity for hearing. Applications of the regulations have been upheld by the courts. *Pfizer, Inc. v. Richardson*, 434 F. 2d 536 (C.A. 2, 1970); *Upjohn Co. v. Finch*, 422 F. 2d 944 (C.A. 6, 1970); *Pharmaceutical Manufacturers Association v. Richardson*, 318 F. Supp. 301 (D. Del., 1970). HW&D is bound by the judgment in the last case cited.

### *III. The Request for a Hearing*

a. *The issues of exemption under section 107(c) of Public Law 87-781 and under 21 U.S.C. 321(p)(1).* The request for a hearing on these issues is denied. The new-drug applications involved had not been withdrawn prior to enactment of Public Law 87-781. They were "deemed approved" under the 1962 amendments to the Act and are subject to withdrawal on the basis of the effectiveness requirements of the amendments.

b. *Lutrexin and Trexonest are new drugs within the meaning of 21 U.S.C. 321(p)(1).* The conclusions of HW&D's affiants that these drugs are not new drugs cannot be accepted. No adequate and well-controlled clinical investigations published in the medical literature have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

The affiants identify 11 studies as establishing the claims made for the drugs. None purports to be an adequate and well-controlled clinical investigation. They may be summarized as follows:

(1) Majewski and Jennings: *Uterine Relaxing Factor for Premature Labor*, *Ob. & Gyn.* 5:649-652 (May 1955); and *Further Experiences with a Uterine Relaxing Hormone in Premature Labor*, *Ob. & Gyn.* 9:322-325 (March 1957) by the same authors are one study. The first paper is a preliminary



study on 20 patients and the latter is the report on enlarged group of 88 patients. The authors acknowledge that results in the total group are less favorable than in the preliminary study, but conclude that the results are encouraging. Concomitant medication was given an unstated number of patients. There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced. Nine patients out of 88 in whom the drug proved ineffective were excluded from the report for "statistical reasons". Six patients received the drug for less than 3 hours, which the authors without explanation considered too short a time for a true test of effectiveness. There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance.

(2) Majewski: Statistical Evaluation in The Reduction of the Incidence of Prematurity (1968) is unpublished. The author claims successful treatment in 86 percent of cases treated in his practice over a 10-year period. Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. The author acknowledges that some patients with medical complications such as placenta praevia were included in the study. Lutrexin is not claimed to have value in the medical or obstetrical complications of pregnancy which occur in a significant percentage of premature births

The paring of live birth percentages by number of pregnancies before and after Lutrexin treatment such as in Table I are all inappropriate. For example, of the 24 cases with one previous pregnancy, 11 live births before treatment and 18 live births after treatment are compared. However, for each of the 18 live births after treatment, an additional pregnancy had elapsed so that the number of previous pregnancies associated with the number 18 is two, not one; as such, the number 18 should be compared with the number 16, the total live births for two previous pregnancies.

The data in Table I does not admit of statistical evaluation by the chi-square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses, e.g., for the one patient with seven previous pregnancies, four live births are correlated, thus ignor-

ing the sample size of one and using an erroneous sample size of four.

(3) Rezek: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luterum in the Treatment of Dysmenorrhea, *Am. J. Ob. & Gyn.* 66:396-402 (August 1953). The report does not state the method of patient selection, nor does it indicate comparability of pertinent variables such as severity or duration of diseases. Concomitant medication is not excluded. No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and investigator bias are provided. The historical controls employed are inappropriate.

(4) Rezek: Lutrexin in the Treatment of Premature Labor, *Ann. N.Y. Acad. Sci.* 75:995-997 (January 1959). The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor. The methods of observation and the recording of results are not explained. No statistical evaluation was presented to show that results claimed are significant in terms of the patient population.

(5) Gratton: The Treatment of Infertility and Prematurity Pregnancy Problems (1968) is unpublished. Patients received numerous concomitant therapies until the fifth month of pregnancy which prevents scientific attribution of results to lututrin therapy. The method of patient selection is unexplained.

Statistically the study lacks adequate design and evaluation. There is no showing that the cases studied are representative of the population to which inferences are made. The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor.

(6) Gray: Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases (undated) is an unpublished report on 15 selected cases the author has treated. No plan or protocol is provided to allow determination of the objectives of the study, the method of patient selection, diagnostic criteria of the condition to be

treated, laboratory tests to be made, the methods of observation and recording of results. The author's review of his records does not constitute an adequate and well-controlled investigation.

(7) Four papers by Dr. Trythall were listed in the attachment to his affidavit. In only one article is lutrexin ever mentioned. The three sentences devoted to the drug provide no information whatsoever except that the author claims to have found it effective in his practice.

The affiants state that double blind investigations of lututrin are unethical because the drug is effective and complications of pregnancy may be life-threatening. The Commissioner does not reach that issue, since none of the historically controlled studies relied upon were adequate and well-controlled investigations.

There are other reasons why HW&D's medical data lack merit, but in view of the above finding their delineation is unnecessary.

c. *The issue of substantial evidence of effectiveness.* The request for a hearing on this ground is denied. The regulations, 21 CFR 130.14, require HW&D to submit a well organized and full factual analysis of the clinical and other investigational data it is prepared to prove at a hearing. The request must set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. HW&D has not attempted compliance with these requirements.

Rather than identify and discuss the efficacy data relied upon to support the claims made for its drugs, the company has merely provided a list, extending to four pages, of practically all materials ever submitted to the Agency and the NAS-NRC. The materials are described, for the most part, in general terms (e.g., "data submitted in connection with New Drug Application for Lutrexin tablets \* \* \*, Lutrexin bibliography \* \* \*, Trexinvest bibliography \* \* \*, reprints and abstracts \* \* \*"). What the Commissioner is required to do is to determine from this material, what HW&D may or may not consider relevant and, therefore, relies upon. In the case bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it

relevant. Because such a procedure is not contemplated by the regulation, the request for hearing is denied for failure to comply with applicable regulations.

Apart from the refusal of HW&D to comply with 21 CFR 130.14, the most basic material in the Lutrexin new-drug application reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it.

The only evidence submitted that lututrin may have biological activity in humans when taken orally is a test on nine women by Jones and Smith in which positive results were reported to have been obtained in six subjects. No plan or protocol was stated. No data on the participating patients was provided. No explanation of procedures for patient selection, or criteria for inclusion in the study, or appropriate laboratory tests before and after administration of lututrin was provided. No statistical analysis showing the test population was of significant size or that results obtained were significant is shown. Moreover, there is no evidence that results claimed have ever been reproduced in humans by other investigators.

Therefore, the Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under the authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effects it is purported or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

Pursuant to the foregoing findings, approvals of the above new-drug applications, and all amendments and supplements thereto, are withdrawn effective on the date of the signature of this document.

Dated: May 31, 1971.

CHARLES C. EDWARDS,  
*Commissioner of Food and Drugs.*

*Petition of Hynson, Westcott & Dunning, Incorporated For a Stay of the Order of the Commissioner of Food and Drugs Withdrawing Approval of the New Drug Applications for Lutrexin and Treximest (36 FR 11763)*

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, FOOD  
AND DRUG ADMINISTRATION

(Docket FDC-D-123)

NDA Nos. 8-986 and 10-144

In the Matter of: LUTREXIN AND TREXINEST HYNSON, WEST-  
COTT & DUNNING, INCORPORATED.

Hynson, Westcott & Dunning, Incorporated ("HW&D") respectfully requests the Commissioner of Food and Drugs for a stay of his order withdrawing approval of the New Drug Applications (NDAs) for Lutrexin and Treximest, pending timely filing by HW&D in the United States Circuit Court of Appeals of a petition that the order of the Commissioner be set aside, and pending the disposition of the petition by the Court. If this request for a stay is refused by the Commissioner HW&D will thereupon file with the Court of Appeals an application for such a stay and hereby requests the Commissioner to stay his withdrawal order pending the decision of the Court of Appeals upon such application.

The order of the Commissioner withdrawing approval of the NDAs is dated May 31, 1971, effective upon that date. The order was published eighteen days later in the Federal Register of Friday, June 18, 1971, when it first became available to HW&D and its counsel.

1. *Safety.* Lutrexin and Treximest were accepted by FDA as safe when the agency permitted the NDAs for the drugs to become effective on December 23, 1953, and March 23, 1956,

respectively. Experience has confirmed the safety of the drugs since the NDAs became effective.

The affidavits of Doctors Bickers, Gratton, Majewski, Rezek, and Trythall, which are before the Commissioner, all testify to the safety (and effectiveness) of Lutrexin. These affidavits are only examples of the many expressions of OB/Gyn physicians who have made known to HW&D their conviction of the safety (and effectiveness) of the drug.

Dr. Willard M. Allen, a member of the NAS/NRC Panel, which evaluated Lutrexin stated, in a letter which is attached to Dr. Dunning's letter to Commissioner Edwards dated January 22, 1970—

The clinical evidence which you have submitted and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended.

Lutrexin, since it contains an active principle which relaxes the uterus should be available for the treatment of premature labor and should continue to be available until such time as a fully rational and effective treatment has been discovered.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multivitamins.

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

The affidavits before the Commissioner and the letter of Dr. Allen show not only that Lutrexin is safe but that there is a need for the drug in OB/Gyn practice.

2. HW&D proposes to seek judicial review of the Commissioner's order because it believes that Lutrexin is safe and effective and should be made available to the many OB/Gyn

physicians who regard it as useful or necessary in their practice. HW&D is entitled by statute to such review. In view of the undoubted safety of the drug, those physicians who desire to use it should not be precluded from such use until the issues here involved have been finally determined. Once the drug is removed from the market it is highly unlikely that it will be practicable to resume its distribution, with the result that it will be unavailable to the many physicians who have, since 1953, found it useful for their patients. Substantial legal and factual questions are involved in this matter. It is submitted that the prohibition of the marketing and use of the drug by physicians who want to use it before these questions are finally resolved would not be reasonable or in the public interest, and the denial of a stay would, under the circumstances, have the effect of a final decision insofar as the future use of the drug is concerned.

3. The stay herein requested is authorized by the Administrative Procedure Act (5 USC 705) pending judicial review when "justice so requires" and is within the contemplation of Rule 18 of the Federal Rules of Appellate Procedure. We believe that, under the circumstances of this case justice requires the stay herein requested.

Respectfully submitted,

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Counsel for  
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Incorporated.

July 1, 1971.



36 F.R. 17371 (August 28, 1971)

FOOD AND DRUG ADMINISTRATION

[Docket No. FDC-D-123; NDA No. 8-986, 10-144]

HYNSON, WESTCOTT & DUNNING, INC.

LUTREXIN TABLETS, TREXINEST TABLETS; NOTICE OF DENIAL OF  
PETITION TO STAY EFFECTIVE DATE OF ORDER WITHDRAWING  
APPROVAL OF NEW-DRUG APPLICATIONS

The petition of Hynson, Westcott & Dunning, Inc. (HW & D) for a stay of the order withdrawing approval of new-drug applications Nos. 8-986 and 10-144 for its drugs containing lututrin is, after consideration of all the data offered by HW & D to support continued marketing of these preparations, denied for the following reasons:

1. Since 1966 HW & D has had repeated opportunities to come forward and present evidence derived from adequate and well-controlled clinical investigations demonstrating that lututrin is effective for its intended uses and has repeatedly failed to provide such data. No acceptable scientific data to support the efficacy claims made for these preparations was presented to either the National Academy of Sciences-National Research Council or the Food and Drug Administration.

2. There is no acceptable scientific data showing that lututrin has any biological activity in humans. To the contrary, there is evidence that lututrin is destroyed by hydrolysis due to the action of the gastric enzymes before it can pass the membrane barrier of the intestinal mucosa and be absorbed into the blood stream.

3. While lututrin is not a highly toxic pharmacologic agent—actually it appears to be inert—its use in patients exposes them to drug therapy without any concomitant possibility of therapeutic benefit.

4. In respect to the drug Trexinest, HW & D did not attempt to offer evidence that either component of that fixed ratio combination drug contributes to the claimed efficacy of the drug.

Dated: August 18, 1971.

SAM D. FINE,

*Associate Commissioner for Compliance.*

[FR Doc. 71-12645 Filed 8-27-71; 8:52 a.m.]



## Petition to Set Aside Order of Commissioner of Food and Drugs

Hynson, Westcott & Dunning, Incorporated, hereby petitions the Court to set aside the Order of the Commissioner of Food and Drugs withdrawing approvals of new drug applications for Petitioner's drugs Lutrexin Tablets and Trexineest Tablets. The Order, which is dated May 31, 1971, recites that it is effective on the date of signature. It was filed with the Office of the Federal Register on June 17, 1971, and was published in the Federal Register of June 18, 1971 (36 FR 11763).

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### *Certified List of Record Pursuant to Rule 17(b) of the Federal Rules of Appellate Procedure*

I hereby certify that following material comprised the record upon which the Order, dated May 31, 1971, was based and upon which judicial review is sought in this proceeding:

1. New Drug Application No. 10-144 (Trexineest) consisting of one file volume totaling approximately 300 pages.

2. New Drug Application No. 8-986 (Lutrexin) consisting of three file volumes totaling approximately 400 pages.

3. Drug Efficacy Study Implementation Announcement regarding Lututrin published in the Federal Register on May 24, 1968 (33 F.R. 7701); 1 page.

4. Letter (with enclosure) dated July 12, 1968, from Bruce J. Brennan and John K. Worley to Herbert L. Ley, Commissioner of Food and Drugs; 4 pages.

5. Letter dated July 23, 1968 from Herbert L. Ley, Commissioner of Food and Drugs, to Bruce J. Brennan and John K. Worley; 1 page.

6. Letter dated July 26, 1968 from Bruce J. Brennan and John K. Worley to Herbert L. Ley, Commissioner of Food and Drugs; 2 pages.

7. Letter dated August 12, 1968 from Herbert L. Ley, Commissioner of Food and Drugs, to Bruce J. Brennan; 2 pages.

8. Notice of Opportunity for Hearing, Hynson, Westcott and Dunning, Inc. Lutrexin Tablets, Treximest Tablets published in the Federal Register on March 22, 1969 [34 F.R. 5556]; 1 page.

9. Letter dated April 18, 1969 from Hynson, Westcott and Dunning, Inc. to Beryl McCullar, Hearing Clerk; 1 page.

10. Letter consisting of 8 pages dated October 16, 1970 from Edward Brown Williams to Beryl McCullar, Hearing Clerk and enclosing the following:

A. Hynson, Westcott and Dunning's Complaint for Declaratory Judgment and Injunctive Relief consisting of 25 pages filed August 19, 1969 in the United States District Court for the District of Maryland (Hynson, Westcott and Dunning, Inc. v. Finch, C.A. No. 21112) including three exhibits: (1) Drug Efficacy Study Implementation [33 F.R. 7701]; 1 page; (2) Notice of Opportunity for Hearing [34 F.R. 5556]; 1 page; (3) Letter of Hynson, Westcott and Dunning dated April 18, 1969, 1 page.

B. Hynson, Westcott and Dunning's Memorandum in Opposition to Defendants' Motions to Dismiss and in the Alternative for Summary Judgment (C.A. No. 21112) consisting of 56 pages, with the following exhibits: (1) Exhibit I. Affidavit of William M. Bickers, M.D., with curriculum vitae (Exhibit A) and list

of publications; 10 pages. (2) Exhibit II. Affidavit of Richard R. Gratton, M.D., with curriculum vitae (Exhibit A) and a copy of paper by Dr. Gratton entitled, "Treatment of Infertility and Prematurity Pregnancy Problems"; 13 pages. (3) Exhibit III. Affidavit of Fred B. Gray, M.D., with clinical report entitled, "Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases"; 11 pages. (4) Exhibit IV. Affidavit of Joseph T. Majewski, M.D., with curriculum vitae and list of publications (Exhibit A), and copies (Exhibits B, C, and D) of papers by Dr. Majewski, entitled, "A Uterine Relaxing Factor for Premature Labor", "Further Experiences with a Uterine Relaxing Hormone in Premature Labor", and "Statistical Evaluation in the Reduction of the Incidence of Prematurity"; 21 pages. (5) Exhibit V. Affidavit of George H. Rezek, M.D., with curriculum vitae and list of publications (Exhibit A), and copies of two papers (Exhibits B and C) by Dr. Rezek entitled, "The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea" and "Lutrexin in the Treatment of Premature Labor"; 16 pages. (6) Exhibit VI. Affidavit of Joseph F. Sadusk, M.D., with curriculum vitae (Exhibit A), list of publications (Exhibit B), and copy of paper (Exhibit C) by Dr. Sadusk entitled, "The Definition of the Efficacy of a Drug Under the Law"; 23 pages. (7) Exhibit VII. Copy of letter dated January 22, 1970, from Hynson, Westcott and Dunning to Commissioner Edwards, with attached copy of letter dated December 10, 1969, from Willard M. Allen, M.D., to J. H. F. Dunning, President of Hynson, Westcott and Dunning (Exhibit A); 12 pages. (8) Exhibit VIII. Commissioner Edwards' reply undated to Dr. Dunning's letter of January 22, 1970; 1 page.

C. Copy of Motion of Plaintiff for Continuance; 4 pages.

D. Affidavit of Sylvester W. Trythall, M.D., dated September 14, 1970, with curriculum vitae and list of publications; 8 pages.

E. Letter dated May 19, 1970, from Commissioner Edwards to Hynson, Westcott and Dunning; 1 page.

F. Letter dated June 10, 1970, from J. H. F. Dunning to Commissioner Edwards; 2 pages.

G. Transcript of Hearing on Defendants' Motions to Dismiss and in the Alternative for Summary Judgment in C.A. No. 21112 (D. Md.); 37 pages.

H. Certified copy of Order of Dismissal entered on September 11, 1970, in C.A. No. 21112 (D. Md.); 2 pages.

11. Order Withdrawing Approval of New Drug Applications 8-986 and 10-144 published in the Federal Register on June 18, 1971 [36 F.R. 11763]; 3 pages.

12. Letter and Petition for a Stay of the Order Withdrawing New Drug Applications 8-986 and 10-144 from Counsel for Hynson, Westcott and Dunning to Beryl McCullar, Hearing Clerk, dated July 1, 1971; 4 pages.

13. Notice of Denial of Petition to Stay Effective Date of Order Withdrawing Approval of New Drug Applications 8-986 and 10-144 published in the Federal Register on August 28, 1971 [36 F.R. 17371]; 1 page.

I further certify that the above named and described materials are being held by me on behalf of the Clerk of this Court, in the Office of the Hearing Clerk, subject to further order of the Clerk of this Court.

[SEAL]

(S) Charles C. Edwards,  
CHARLES C. EDWARDS, M.D.,  
Commissioner of Foods and Drugs.

### ABSTRACT

In the treatment of infertility and prematurity problems, uterine irritability and contractility are part of a complex syndrome which must be recognized early if viability of the fetus is to be obtained.

The results obtained over approximately a ten-year-period in 219 patients with a history of from 1 to 10 (for the most part 1 to 5 previous pregnancy complications) are presented.

The improved birth rate following institution of aggressive therapy is shown.

## *The Treatment of Infertility and Prematurity Pregnancy Problems*

RICHARD R. GRATTON, M.D.

In the practice of infertility, gestation, once established in the previously infertile female, must be maintained and the fetus brought to viability.

The evaluation of any treatment or treatments requires a comparison with the spontaneous fertility rate. This fact has been a major stumbling block in the assessment of regimens used to treat infertility.

Since the etiological factors which may cause the premature emptying of the uterus are many, it is logical to assume that no one type of treatment can be expected to take care of all causative factors. Careful analysis of all probable causal factors results in more specific and intensive treatment of them.

Uterine irritability and contractility are part of a complex syndrome which must be recognized early if a threatened premature delivery is to be avoided.

Our practice deals for the most part with difficult problem cases and every pregnancy is considered as a possible cause of habitual abortion or premature labor. Prior to the institution of the use of Lutrexin as the major drug in treating these problem cases, less than 50% viable babies resulted. With the use of Lutrexin, a significant improvement occurred—about 80% viable babies were obtained.

### Materials and Methods

Prior to the introduction of Lutrexin therapy, patients were treated as follows: Multivitamins, Vitamin C 250 mgs. daily, Thyroid, Progesterones—orally, buccally or vaginally twice weekly, Stilbestrol 25 mg. (E.C.) 1-4 tablets per day.

Patients were treated with Lutrexin as follows: In early pregnancy, if the uterus was irritable or retroverted and knee-chest exercises and/or a pessary was used, the Lutrexin dosage was 1 tablet twice a day, or 1 tablet four times a day.

At 5-6 months of pregnancy, if uterine contractions occurred, the amount of Lutrexin was increased to as much as 8 tablets per day.

In premature labor, the dosage schedule of Lutrexin was 12 tablets every hour for 8-24 hours. If contractions ceased, Lutrexin was maintained at 8-24 tablets each day until term.

Other treatment given included: (1) Provera 10 mg.  $\frac{1}{2}$  or 1 tablet once or twice daily; (2) Vitamin C 250-500 mg. daily; (3) Multivitamins daily; (4) Thyroid grains 1-2 daily in the first three months of pregnancy; (5) Progesterone in oil 50 mg. I.M. every 1-2 weeks until the fifth month of pregnancy.

### Results

Although there were 286 patients treated as described under Materials and Methods, 67 of these had not been pregnant before and were excluded from Table I, which presents the patients on the basis of the number of previous pregnancies and live births prior to the inception of Lutrexin therapy as well as the live births resulting when patients were treated with Lutrexin.

In Table II, the data of the previous Table I have been combined to facilitate statistical evaluations. It can be seen that in the 219 patients with a total of 446 pregnancies, there were only 46% live births prior to the use of Lutrexin. Following the administration of Lutrexin, the percentage of live births in these same patients was 79.8% with a probability of .001.<sup>1</sup> Probabilities ranging from .001 to .05 were observed in women with one to five previous pregnancies who had been treated with Lutrexin. No statistical tests for significance were made with six or more pregnancies because of the small sample.

### Discussion

After using Lutrexin in a small number of problem cases and noting the apparent beneficial effect, it was decided to utilize this drug in all cases of premature labor, threatened abortion and habitual abortion. Experience gained over approximately ten years has amply shown the value of Lutrexin in the treatment of such patients. Before using this drug, only 46% live births were obtained in 446 pregnancies, whereas with the use of Lutrexin, 79.8% live births were achieved. The differences noted with, and without, Lutrexin were highly significant ( $P=.001$ ) in the entire study herein reported. Signifi-

cant differences ( $P=.001$  to  $.05$ ) were observed in patients with one to five previous pregnancies.

In this study, the patients have served as their own controls. This practice has been criticized by Goldzieher.<sup>2</sup> On the other hand, the use of double-blind studies, although very satisfying from a purely scientific point-of-view may, as indicated by Allen<sup>3</sup> "violate morality as well as common sense". Having experienced relatively poor results in the case of these difficult problem cases in the past, the beneficial effects resulting from the administration of Lutrexin to the first number of cases on which it was tried, it seemed desirable to extend it to others. The denial of such treatment to others to obtain more scientifically acceptable data was unacceptable in view of the safety of the drug as well as reports of its effectiveness.

Another argument that might be made as to the validity of the data is that there have been some unknown factors that have suddenly caused the patients to show a higher percentage of live births than observed before, unrelated to Lutrexin therapy. If such factors were operative, it might be anticipated that there would be some lowering in the prematurity rate as part of an overall improvement in the pregnancy state. However, no evidence for this was found. The prematurity rate in the United States has been about 6-7% for many years.<sup>4</sup> This is quite similar to the rate prevailing in the San Francisco area from which the patients in this study were drawn.

No other factors could be found that might explain the significant increase in percentage of live births other than the use of Lutrexin.

It is felt that the good results obtained in this study are related to the institution of Lutrexin therapy as early as possible, particularly when there is a history of repeated early abortions or premature labors when there is no cervical incompetence or when retroversion of the pregnant uterus is found.

### Summary

1. The results obtained in the treatment of 219 women with a past history of prematurity, threatened and habitual abortion with Lutrexin are presented.

2. A live birth rate of 80% was obtained with the use of Lutrexin as compared to 46% prior to the use of this drug.

## References

1. Maltland, D.: CANADA JOURNAL OF RESEARCH, 26:1-106, February 1948.
2. Goldzieher, J. W.: J.A.M.A., 188:131-134, May 18, 1964.
3. Allen, W. M.: ROCKY MT. MEDICAL JOURNAL, 62: 31-35, August 1965.
4. Majewski, J. T. and Pennings, T. L.: OBSTETRICS & GYNECOLOGY, 5:649-652, May 1955.

TABLE I.—*Presentation of study group with respect to previous pregnancies live births and results following Lutrexin treatment*

Prior to Treatment with Lutrexin					Following Treatment With Lutrexin	
No. of Cases	No. Previous Pregnancies	No. Live Births	Total Pregnancies	Total Live Births	Live Births	Deaths
41	1	0	41	0	27	14
65	1	1	65	65	54	11
16	2	0	32	0	13	3
21	2	1	42	21	18	3
20	2	2	40	40	17	3
9	3	0	27	0	6	3
8	3	1	24	8	8	0
5	3	2	15	10	5	0
5	3	3	15	15	4	1
3	4	0	12	0	1	2
5	4	1	20	5	5	0
3	4	2	12	6	3	0
3	4	3	12	9	3	0
1	5	0	5	0	1	0
4	5	1	20	4	2	2
3	5	2	15	6	3	0
1	5	3	5	3	1	0
2	6	2	12	4	2	0
1	6	3	6	3	0	1
1	7	0	7	0	0	1
1	9	3	9	3	1	0
1	10	3	10	3	1	0
219					175	44



TABLE II.—EVALUATION OF EFFECTIVENESS OF LUTREXIN THERAPY

No. of Cases	Prior to Treatment with Lutrexin				After Treatment with Lutrexin			
	No. Previous Pregnancies	Total Pregnancies	Total Live Births	% Live Births	Total Live Births	% Live Births	Chi Square	Probability
106	1	106	65	61.3	81	76.4	5.2	.05
57	2	114	61	53.5	48	84.2	14.2	.001
27	3	81	33	40.7	23	75.2	14.3	.001
14	4	56	20	35.7	12	85.7	11.8	.001
9	5	45	13	28.9	7	77.8	5.7	.02
3	6	18	7	38.9	2	66.7	-----	-----
1	7	7	0	0.0	0	0.0	-----	-----
1	9	9	3	33.3	1	100.0	-----	-----
1	10	10	3	30.0	1	100.0	-----	-----
219	-----	446	205	46.0	175	79.8	-----	.001

The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *The Treatment of Infertility and Prematurity Pregnancy Problems* (1968, unpublished).

Date: March 11, 1970.

/s/ Richard R. Gratton, M.D.  
RICHARD R. GRATTON, M.D.

### *A Uterine Relaxing Factor for Premature Labor*

[Reprinted from Vol. 5, No. 5, May 1955]

#### OBSTETRICS AND GYNECOLOGY

J. T. Majewski, M.D., and T. Jennings, M.D.

Premature delivery occurs in 6 to 7 percent of total births. Prophylaxis against premature labor seems desirable to prevent the difficult task of caring for a premature infant.

In recent years, interest has increased in the effects of hormonal changes on the initiation of labor. In this study, a uterine relaxing factor (LUTREXIN) was administered clinically to 21 patients judged to be in premature labor and succeeded in giving a favorable result in 80% of the cases. Our results show one method of treatment that may lead to the salvage of a number of infants.

Krantz, Bryant, and Carr in 1950 demonstrated the ability of a substance found in aqueous extracts of sow corpora lutea to diminish the tone and abolish contractions of the guinea pig uterus in situ. This material has been studied chemically by Felton, Frieden, and Bryant (1953) and its effect in the treatment of dysmenorrhea has been investigated by Rezek and by Jones and Smith. The present study relates to our work in utilizing this material in attempts to reduce the high fetal death rate associated with premature labor.

It is generally agreed that between 6 and 7 per cent of total births have, consistently, been premature. In the hospital in which this study was conducted, the prematurity average is 9.7 per cent by maternal history and 6.2 per cent by weight. The criterion of prematurity is a birth weight less than 2300

From the Department of Obstetrics and Gynecology, Marquette University, School of Medicine, Milwaukee, Wisc.

Gm. The fetal death rate also closely parallels that of other institutions, being 99 per cent for infants of 750 Gm. and 7 per cent at 2000 Gm. or over. The total death rate is calculated as 30 per cent.

The solution to this problem of a high premature fetal mortality has been elusive. The ideal method seems to be, as Potter states, that of prophylaxis against premature labor, thus circumventing the very difficult task of caring for a premature infant.

Many theoretical explanations have been given of the mechanics of the onset of labor, but as yet all have remained hypothetical. These theories encompass almost every aspect of parturition. A few attribute to the uterus, with its increasing size and growing irritability, the responsibility for producing spontaneous labor. Other theories are concerned with the environment of the cervix and lower segment of the uterus near term, the carbon dioxide content of the blood, and senility of the placenta.

In recent years, interest has increased in the effects of hormonal changes on the initiation of labor. There have been several revealing studies on this subject, including an important observation by Snyder. He prolonged the duration of pregnancy in the rabbit by inducing ovulation near term and concluded that the retention of the fetus in the uterus is under hormonal control and that parturition coincides with the termination of the life-cycle of the corpus luteum. In a parallel study, Heckel and Allen found that 1.5 mg. progesterone injected subcutaneously in rabbits not only may delay but even prevent parturition. Despite the evidence presented by these authors it is our belief that the trigger mechanism of labor is multiple, being hormonal, fetal, placental, and local in uterine and cervical changes.

#### MATERIAL

In this preliminary study, the uterine relaxing factor was administered to 21 patients. All but 2 of the patients were treated in the hospital. The 2 exceptions were given medication and treated at home with no restriction of activity. Only individuals clinically adjudged to be in labor were selected, the choice being made by the attending physician and the

resident. Patients who were well advanced in labor (beyond 3 cm. dilatation) were not given the uterine relaxing factor. Those who terminated their pregnancy prematurely because of abruptio placentae, or central placenta previa likewise were excluded from this study. Other than these restrictions, there were no attempts to exclude patients for such reasons as ruptured membranes or monstrosities.

### RESULTS

The hospital wherein the study was conducted has, as stated, a premature birth rate of 9.7 per cent by length of gestation and 6.2 per cent by weight. During a four-month period in 1953, the premature birth rate by history was 9.7 per cent in 1601 deliveries. During the same period, there were 101 premature births by weight, or 6.3 per cent. During this study there were, in a comparable period during 1954, 154 births premature by history in a total of 1631 deliveries, for a percentage of 9.4. In our series of patients using the uterine relaxing factor the number of premature deliveries by weight was reduced during these four months to 80 (4.9 per cent)—a saving of 21 premature deliveries. These included both vaginal and abdominal deliveries.

TABLE 1.—Summary of experimental series

Case	Pains on entrance		Cervix			Presenting part	Station	Membrane	Bloody show
	Type	Freq.	Duration (hr.)	Dilat.	Efface.				
1	Mod.	2 min.	1	1 Fb.	Soft	Vertex	-3	Intact	0
2	Mod.	2 min.	4	1 Fb.	Thick	Vertex	-1	Intact	0
3	Mod.	3 min.	4	Not reached		Vertex	-3	Intact	±
4	Mod.	10 min.	9	2 Fb.	Soft	Vertex	0	Intact	0
5	Mild	Irreg.	3	1 Fb.	Thick	Vertex	-3	Intact	0
6	Mild	Irreg.	2	Closed	Thick	Vertex	-3	Intact	±
7	Mild	Irreg.	2	Closed	Thick	Vertex	-3	Intact	±
8	Mild	2-3 min.	3	1 Fb.	Thick	Vertex	-1	Intact	0
9	Mild	Irreg.	Indef.	1 Fb.	Thick	Vertex	-3	Intact	±
10	Mild	4-6 min.	6	Closed	Thick	Vertex	-1	Intact	0
11	Mild	15 min.	?	1 Fb.	Thin	Vertex (twins)	0	Bulging	±
12	Mild	Irreg.	3	2 Fb.	Thick	Vertex	-1	Intact	±
13	Mild	5 min.	2	2 Fb.	Thin	Vertex	-3	Intact	±
14	Severe	3 min.	5	1½ Fb.	Soft	Vertex	0	Ruptured	±
15	Mod.	5 min.	4	No.	Rectal			Intact	±
16	Mod.	5 min.	3	1½ Fb.	Soft	Vertex	-1	Intact	±
17	Mild	5 min.	6	1½ Fb.	Soft	Vertex	0	Intact	0
18	Mod.	4 min.	4	2 Fb.	Soft	Vertex	0	Ruptured	0
19	Mild	Irreg.	Indef.	1 Fb.	Soft	Vertex	-2	Intact	0
20	Mild	Irreg.	Indef.	1 Fb.	Soft	Vertex	-3	Intact	0

NOTE: Table 1 continues on page 96.

TABLE 1.—*Summary of experimental series—Continued*

Case	Grav.- Para.	E.D.C.	Gesta- tion (wk.)	Other sedation	Outcome	Date of delivery	Wt. of baby (Gm.)	Wt. of pre- vious baby (Gm.)
1	3-2	6-8-54	35	None	Pains lasted 3 da.	39 wks	2792	2807-3090.
2	5-4	3-1-54	35	None	Pains lasted 24 hr	41 wks	3459	2353-2722.
3	5-3	3-5-54	38	None	Pains lasted 8 wk	41 wks	3459	2495-3118.
4	1-0	5-1-54	30	None	Pains lasted 20 hr	33 wks	2325	None.
5	5-3	3-28-54	34	None	Pains lasted 15 hr	39 wks	3685	3062-3629.
6	2-1	4-7-54	27	None	Pains lasted 12 hr	39 wks	3289	2863.
7	3-2	2-15-54	25	None	Pains lasted 24 hr	42 wks	3430	Unknown.
8	3-2	1-20-54	28	100 mg.	Pains lasted 7 hr	38 wks	2920	2211-2948.
9	2-1	1-1-54	32	None	Pains lasted 8 hr	39 wks	3260	3402.
10	3-2	12-31-53	32	None	Pains lasted 6 hr	39 wks	2920	3289.
11	2-1	1-23-54	26	None	Pains lasted 3 hr	28 wks	624, 652	2920.
12	2-1	2-21-54	34	None	Pains lasted 3 hr	38 wks	2892	3260.
13	3-2	4-1-54	34	None	Pains lasted 3 hr	37 wks	2070	2240-2948.
14	2-0	3-8-54	24	None	Delivery 4 hr	24 wks	907	
15	5-4	4-28-54	34	None	Delivery 3 hr	34 wks	1531	2580-3402.
16	2-0	3-29-54	22	None	Delivery 5 da.	22 wks	680 Stillborn	
17	1-0	2-27-54	32	None	Pains lasted 5 hr	38 wks	2325	
18	1-0	3-6-54	36	None	Delivery 10 hr	36 wks	2041	
19	3-2	4-28-54	30	None	Pains lasted 5 hr	39 wks	3062	1928-2381.
20	6-1	6-1-54	23	None	Pains lasted 2 hr	29 wks	1417	3345.

The plan of dosage was derived by clinical trial and error. Upon admission the patient was prepared for normal vaginal delivery. The perineum was shaved and cleaned, and the patient was placed in bed. Enema was excluded. No attempts were made to inform the patients of the therapy or of the desired end results. No attempts were made to give the patients sedation, although some received small doses of barbiturates. The pains were recorded, in most instances, by competent observers who evaluated the contractions clinically rather than by relying upon the patient's statement.

The dosage of the uterine relaxing factor, after a few trials, was fixed at 4000 units initially, followed in one hour by 3000 units, and by 1000 units hourly thereafter until contractions ceased both clinically and symptomatically. All doses were given orally. No side effects were observed.

The results are tabulated in Table 1. There were 4 deliveries in spite of the therapy, giving a favorable result in 80 per cent of the cases. Some patients were of sufficient interest to deserve separate mention.

Case 11 was a multipara with a multiple pregnancy, the first baby being in vertex presentation at zero station. Lutrexin\* was started upon entry to the hospital, at which time she was 1 fingerbreadth dilated with membranes bulging. The pains continued for approximately 3 hours and gradually subsided. At the time when contractions ceased, the cervical os was 3 cm. dilated with membranes still bulging. The patient was kept under therapy and allowed to ambulate. She was discharged after one week, only to return in another and deliver twins of 624 gm. and 652 gm. weight. As long as the patient was under the uterine relaxing factor the uterus was quiescent. However, when therapy was discontinued, uterine irritability and eventual labor returned.

Case 19 was a gravida III who had been previously delivered of a 2381 gm. baby by cesarean section because of cephalopelvic disproportion. Her second delivery, performed vaginally, was of an infant weighing 1928 gm. at 34 weeks' gestation. During the third pregnancy she noted frequent contractions and irritability of the uterus at 30 weeks. This was the same pattern that had occurred with the two previous pregnancies.

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\*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland.

She was placed on Lutrexin therapy at home with no restriction of activity, and her pregnancy was terminated by an elective cesarean section at 39 weeks, the infant weighing 3062 gm. at birth. In this patient, it is interesting to note, if therapy was not given the contractions would become noticeable.

It is, of course, true that Hicks' sign and the softening tendency of the cervix in the last trimester may confuse the picture. Some of our patients may have been experiencing "false labor" pains. There have been in the past and there undoubtedly will be in the future many women saved from premature delivery by watchful expectancy and bed rest. But even after all these allowances have been made, we still feel that our figures have real significance. If the premature birth rate can be reduced the number of salvaged babies soon will be of the utmost importance.

The purpose of this paper is not to propose the uterine relaxing factor as a panacea for all evils connected with premature labors. There are too many factors, including the emotional, concerned in the precipitation of early labor for one remedy to be sufficient. However, our results show one method of treatment that may lead to the salvage of a number of infants.

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The undersigned hereby certifies that the foregoing is a true and correct copy of a paper authored by him and T. Jennings, M. D. entitled *A Uterine Relaxing Factor for Premature Labor*, which was published in *Obstetrics and Gynecology*, Volume 5, No. 5, May, 1955.

J. T. MAJEWSKI, M. D.

Date: .....

*Further Experiences With a Uterine-Relaxing  
Hormone in Premature Labor*

J. T. Majewski, M.D., and T. Jennings, M.D.

An enlarged study was made of the effectiveness of the uterine relaxing hormone LUTREXIN® in premature labor. Contractions were halted in 54 of 79 patients, or 68.4%.

Obstetricians have long sought a means of controlling prematurity, which is believed to cause half of the 150,000 neonatal deaths recorded in the United States each year. Because the etiologies of labor remain unknown, despite the many theoretical explanations advanced, the control of prematurity, once labor has begun, has been unsuccessful.

In an earlier publication we discussed the use of the uterine-relaxing hormone found in the aqueous extracts of the sow corpora lutea in an attempt to halt premature labor in a series of 20 patients.<sup>1</sup> We were able to report success in 16 patients (80 percent). It was decided to continue the project and we are now prepared to report the use of the uterine-relaxing hormone in an additional 68 patients. While results in the total group of 88 patients are somewhat less favorable than in the smaller group alone, they are encouraging.

<sup>1</sup> From the Department of Obstetrics and Gynecology, Marquette University School of Medicine, Milwaukee, Wis.  
Lutrexin for this study furnished by Hynson, Westcott & Dunning, Inc., Baltimore, Md.

## MATERIAL

Eighty-eight patients, both primiparas and multiparas, who were clinically judged to be in labor before the thirty-eighth week of pregnancy, received the uterine-relaxing factor. Evaluation of the patient in labor proved to be the most difficult part of the study. A progression of cervical dilatation, effacement of the cervix, or a progressive descent of the presenting part were deemed indications of "true" labor. In an attempt to exclude patients in false labor, those experiencing grossly irregular uterine contractions, simple backache, an isolated bloody show, or general bearing-down sensations of the pelvis were not given the medication. Patients who entered the hospital with a cervical dilatation of 3 cm. or more were judged to be well advanced in labor and were excluded from the study. The patient's emotional condition was not taken into consideration in the selection of subjects. Those individuals whose labors were complicated by an abruption placentae or a placenta previa are not included in our statistics, since continuing a pregnancy under these conditions is of doubtful value and at times hazardous.

Not all patients who entered the hospital in premature labor were subjects of this study since this hospital is an institution of private care and the final choice rested with the attending physician.

Two of the patients included in the study were not under hospital supervision, but were treated at home; they were ambulatory and were not restricted in activity.

## METHOD

When a patient entered the hospital in premature labor she underwent the usual preparations for vaginal delivery except that no enema was given. No effort was made to inform her of the desired result of the therapy.

The uterine-relaxing hormone Lutrexin\* was administered orally according to the plan worked out in our preliminary study. An initial dose of 4000 units was followed in 1 hour by 3000 units of 1000 units each hour thereafter until uterine contractions were eliminated.

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\*Hynson, Westcott & Dunning brand of lututrin.

TABLE 1.—*Response to Therapy*

[Percentages Based on Size of Groups at Various Weeks of Gestation]

Weeks of gestation	No. patients treated	Labors halted		Labors not halted	
		No.	%	No.	%
Up to 30.....	28	18	64.3	10	35.7
30-32.....	17	11	64.7	6	35.3
32-34.....	15	12	80	3	20
34-36.....	14	9	64.3	5	35.7
36-38.....	5	4	80	1	20

Whenever possible patients receiving the uterine-relaxing hormone were divorced from all other medications. In some patients it was necessary to continue uterine-relaxing-hormone therapy for as long as it was desirable to postpone contractions.

## RESULTS

Uterine-relaxing-hormone therapy successfully halted uterine contractions in 54 of 88 patients studied. For statistical purposes we have eliminated 9 patients in whom the medication was ineffective. Six of these were under the influence of the uterine-relaxing hormone for less than 3 hours before delivery. This we believe is too short a time to be a true test of the medication's effectiveness. The others eliminated delivered an anomalous fetus or had a prolapse of the umbilical cord, conditions in which a merely prolonged pregnancy would have had no value.

Table 1 presents the response of the entire study using the corrected total of 79 patients. Here the percentages are figured on the size of the groups at the various periods of gestation, rather than on the total number of patients in the study. Therapy proved successful in about 64 per cent of the patients whose pregnancies threatened to terminate before the thirty-second week. Other percentages listed may not be truly indicative of response because of the small size of the groups involved.

It should be noted that 45 of the 79 patients (56 percent) entered the hospital before the thirty-second week. Since delivery at this time almost universally connotes fetal disaster,

it is gratifying to note that 29 (64 per cent) of these patients were prevented from delivering at this precarious period despite the fact that labor would not be halted in 16.

Eleven of the 25 babies delivered prematurely when the uterine-relaxing hormone failed to halt labor weighed between 454 and 908 Gm. (Table 2). This weight is normal for babies born during the early part of the last trimester, when the majority of premature labors in our series occurred. The criterion of prematurity is a birth weight of less than 2300 Gm.

The subject of Table 3 is the length of labor in the 25 patients whose uterine contractions were not controlled by the uterine-relaxing hormone. It will be noted that the medication did not appear to lengthen labor in these patients. The length of time during which the uterine-relaxing hormone was administered and the dosage did not seem to be primary factors in the success or failure of the medication in halting labor.

Table 4 compares the total number of premature survivals, stillbirths, and neonatal deaths during the 15-month period the study was in progress. Group I represents those treated with the uterine-relaxing hormone. The increase in survival rests with the fact that labor was delayed, allowing infants to more closely approach maturity.

TABLE 2.—Weights of babies delivered when uterine-relaxing hormone failed to halt labor

Weight (Gm.) :	Number
Up to 454.....	3
545-908.....	11
908-1362.....	4
1362-1816.....	4
1816-2270.....	3
2270-2500.....	0

TABLE 3.—Length of labor following institution of therapy in 25 unsuccessful attempts

Labor time :	Number of patients
4 hours.....	7
4-8 hours.....	3
8-12 hours.....	6
12-24 hours.....	6
28 hours.....	1
36 hours.....	1
5 days.....	1

TABLE 4.—*Premature births during a 15-month period*

	Group I*		Group II	
	No.	%	No.	%
Premature survivals.....	69	78.4	220	71.2
Premature stillbirths.....	5	5.7	23	7.4
Premature deaths (neonatal).....	14	15.9	66	21.4
Total premature births.....	88	100.0	309	100.0

\* Patients treated with uterine-relaxing hormone.

During the study 397 patients delivered prematurely. In a comparable length of time prior to the study there were 404 premature births. In Table 5 we see a comparison by weight of both groups, with Group I representing the study period. We believe it is significant that, while the total deliveries remains about the same, there is a reduction of Group I in the 2 lowest weight brackets. Weight is of great importance, of course, since a premature infant's chances of survival usually parallel his approach to normal birth weight.

TABLE 5.—*Premature totals*

	500-999 Gm.	1000-1999 Gm.	2000-2500 Gm
Group I*.....	42(10.5%)	108(27.2%)	247(62.3%)
Group II.....	49(12.1%)	125(31.0%)	230(56.9%)

\* 379 cases, of which 88 were treated with Lutrexin.

#### DISCUSSION AND CONCLUSIONS

The results of the study recently completed are somewhat less favorable than the results of our preliminary study. In the earlier study the uterine-relaxing hormone halted labor in 16 of 20 patients (80 per cent). In our latest study, which includes the 20 studied earlier, the uterine-relaxing hormone halted contractions in 54 of 79 patients (68.4 per cent).

We found that it was not always possible to postpone labor as long as was desirable. In some patients contractions would return in a period of 4 to 6 weeks and delivery would follow

despite therapy. However, by delaying delivery for several weeks we were able to give 54 babies a longer time to gain weight and to develop within the uterus, thus increasing their chances of survival and lessening the possibility of their suffering from the congenital diseases so often associated with prematurity.

The effectiveness of the uterine-relaxing hormone varies greatly with the individual patients. When it halts labor, it does so in an average of 4 to 6 hours. When it fails to halt labor, it leaves the contractions completely unaffected. In some cases we found it necessary to continue uterine-relaxing-hormone administration in order to keep the uterus quiescent. When therapy was discontinued uterine contractions returned in these patients.

It is noteworthy that when the uterine-relaxing hormone fails, it does not complicate delivery by prolonging labor. No irregular contractions were noted following the administration of the hormone. This would seem to indicate that some unknown factor, antagonistic to the medication or capable of neutralizing its effects, is produced in the bodies of some patients, or perhaps in all patients, at some stage of labor. Another explanation may be that the uterus itself reaches a point in labor when it becomes unresponsive to medication.

We found no side effects either in the patients who were hospitalized or in those who received treatment at home. Voluntary muscles were unaffected. Bowel habits in the ambulatory patients remained the same, which would indicate that the smooth musculature of the gastrointestinal tract was likewise unaffected.

The uterine-relaxing hormone was found to be helpful in relieving Braxton Hicks contractions, which may become somewhat distressing during the last trimester.

The use of the uterine-relaxing hormone is not suggested as a remedy in all instances of threatened premature delivery. It is a temporary measure which may postpone delivery to a more desirable time. We believe that only when the true etiologies of labor are discovered can true therapeutic agents be developed.

It appears that premature labors in otherwise normal women are frequently precipitated by temporary conditions, such as

extergenic pressure on the uterus, emotional excitation, excessive carbon dioxide in the blood following strenuous activity, and perhaps even uncontrolled intestinal peristalsis. If such a condition were present for a sufficient time, it seems possible that cyclic contractions could develop and lead to true labor. It is in the control of uterine contractions under such circumstances that the uterine-relaxing hormone can be most useful.

### SUMMARY

In an enlarged study on the uterine-relaxing hormone, contractions have been halted in 54 of 79 patients, a total of 68.4 per cent. In our earlier small series, labor had been halted in 16 or 20 patients. By delaying delivery for several weeks we were able to give 54 babies a longer time to gain weight and develop within the uterus. The effectiveness of the uterine-relaxing hormone varies greatly with the individual patient. When it halts labor it does so in an average of 4 to 6 hours. When it fails to halt labor, it leaves the contractions completely unaffected.

No side effects were noted in any of the patients who received this therapy. It can be concluded that Lutrexin is successful in controlling uterine contractions, thus reducing the fatality rate for premature infants.

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The undersigned hereby certifies that the foregoing is a true and correct copy of a paper entitled *Further Experiences with a Uterine-Relaxing Hormone in Premature Labor* authored by him and T. Jennings, M. D., which appeared in *Obstetrics and Gynecology*, Volume 9, No. 3, 322, (March, 1957.)

(S) Joseph T. Majewski, M.D.

(S) JOSEPH T. MAJEWSKI, M. D.

Date March 5, 1970.

## *Statistical Evaluation in the Reduction of the Incidence of Prematurity*

(By J. T. Majewski, M.D.)

Prematurity takes a devastating toll among newborn infants. Neonatal mortality rates for the years 1957 through 1966 ranged from 19.1 to 17.2 per 1,000.<sup>1</sup> In studies encompassing as many as 10,000 deliveries, the causes of prematurity were obscure in 60 to 70% of these cases.<sup>2, 3</sup> Because of the implication of these obscurities in his practice, the pediatrician is developing an entire specialty for the care of premature infants. A large number are normal infants who would have had a much better chance for life had they been born at or closer to term. As our ability to care for the infant increases, greater emphasis must be given to increased gestational time for threatening prematurity without jeopardizing the health of mother or infant. By adding to the precious days of gestation, we thus can further assure that not only the life of the infant may be salvaged, but the infant when born, because of added length of uterine incubation, is not plagued with the added misfortunes of mental variations, such as cerebral palsy, physical discoordination or a lessening of the acute definition of the major senses. In this consideration, it may be also admitted that it is nebulous at least to judge, predict, or accurately evaluate any clinical regime, because all are subject to human interpretations. However, certain criteria were employed in this evaluation, and crude as they may be, they are the only measuring devices that are available.

Usually the placebo double-blind study affords the ideal comparison to establish the validity of experimental results. The double-blind study is now academically "sacred", and other types of evaluations too often are not recognized as investigative. In clinical evaluations, the clinician is frequently encompassed in decisions which violate the rules of clinical morality. For instance, in lobar pneumonia, no clinician could risk treating alternating cases with an antibiotic and a placebo. To the clinician concerned with premature labor, it is doubtful that a double-blind study is of choice, and, under such conditions, he could violate sound medical ethics. During his recent tenure as Director of the Bureau of Medicine of the Food and Drug Administration, Dr. J. F. Sadusk, Jr., recognizing this difficulty, stated in part, "The use of other disciplines, such as statistics,



may provide the extra support to make the study an acceptable and convincing one." (4) Properly used and interpreted, statistics are one of the most powerful tools in the scientific armamentarium of the practicing physician.

Prematurity is undeniably present in 5 to 7% of all births, and the fetal wastage is definitely increased if these deliveries occur nearer to the age of viability, which has been stated at the 26th to the 28th week. There have been two papers published by the author, the first in 1955<sup>5</sup>, and the last in 1957<sup>6</sup>. A therapeusis other than symptomatic therapy of a regime of Lutrexin was initiated on those who entered labor prematurely. This regime was tried and successfully, I believe, in controlling the labors and, thus, decreasing the fetal catastrophies. Work at the inception of this undertaking was being completed by Dr. G. H. Rezek<sup>7</sup> of Chicago, Illinois, on the usage of Lutrexin on patients who presented themselves with dysmenorrhea. A logical conclusion was drawn that this medication could be employed to control uterine cramps early in pregnancy. If it could control the rhythmical cramp-like action of the uterus in a non-pregnant stage, it might do the same in early labors. No solicitation by the manufacturer was made. The study was done with the cooperation of the Obstetrical department of St. Joseph's Hospital and Marquette University, Milwaukee, Wisconsin, and all of the results of the two papers were conducted by various members of the obstetrical residents staff and other interested staff members, all duly qualified diplomates of the American Board of Obstetrics and Gynecology.

In essence this report draws the clinical conclusion that the uterine relaxing hormone, Lutrexin, was effective in stopping labor in 86.7% of 75 patients who had previously, without this drug, given a salvage rate of only 51.9%. Further, a brief description of thirteen (13) primiparas who were treated with Lutrexin is given. Eleven of these or 84.6% delivered viable babies. It should be noted that when the hormone halted labor the effectiveness was noted in four to six hours, and when it failed, the labor progressed normally with no side effects. In fact, no untoward effects have been noted by the mother or the infant.

#### DIAGNOSIS OF LABOR

The diagnosis of labor was dictated by the influence the contractions had upon the cervix. Initially, the patients that were used in this study were hospitalized and the progress duly re-

corded and observed by highly trained residents and the obstetrical nurses of the department. The mere statement of contractions by the patient was no criterion. The contractions had to be observed for length and duration and recorded, and the ultimate cervical dilatation had to be noted before the patient would be stated to be in labor. If the patient had cramps, but no effacement, dilatation of the cervix or both, she was not adjudged to be in labor. Placebo or pills for a double-blind study were not used because of hundreds of articles, and the hospital's own statistics, which had remained constant through the years, were used as comparison. The patient could not volunteer information. It had to be observed or it was not accepted. In this study, only patients who reached the 26th week of pregnancy, with effacement of the cervix accompanied by dilatation, were included. No patient was thought to be beyond 38 weeks gestation, or 2 weeks prior to the estimated date of confinement.

The uterine relaxing hormone lututrin\* was administered orally, 12,000 units stat, followed by 9,000 units hourly until contractions ceased, or until delivery or abortion occurred. The only ancillary medication given to any patient was a small dose of Demerol, which never exceeded 50 mg. No patient received more than two such injections.

#### REPORT OF CLINICAL RESULTS

Generalizations gleaned from the study show that there was an 86.7% salvage rate among women who were multiparas, and 84.6% among primiparas, for a general survey of 86.4% success in the 88 patients (see Tables I and II). Chi square was calculated for the group of multiparas, giving a result that was highly significant,  $P < .001$ .

There were three sets of twins in this study, and two were successful. The only unsuccessful attempt was to the first wife of the author, who went into labor at 32 weeks and delivered in 10 hours, despite the attempt to thwart labor.

Five (5) of the multiparas were subjected to circlage suture; four of these carried to term. The one failure was a patient who was sutured approximately the 10th week of gestation; this pregnancy was terminated suddenly by an abruptio placenta. Furthermore, this patient has been pregnant 7 times. Although this individual delivered a normal infant on first pregnancy.

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\*Lutrexin, Hynson, Westcott & Dunning, Inc., Baltimore, Md.

subsequent pregnancies aborted or delivered spontaneously about the 20th to 26th week of gestation. Presently, this same individual is about 5 weeks from term after a Mersilene tape suture was employed when examination revealed bulging membranes and definite dilation of the cervix. Although the number of case histories in this category is small (5), the salvage of 80% of these pregnancies correlates well with the 81.5% reported by Jeremias and Trythall in a larger series.<sup>8</sup> On the other hand my results contrast with a 63% salvage rate recently reported with the use of a progestin and isoxsuprine hydrochloride, and this is a significant contrast to the 25% salvage rate obtained prior to treatment.<sup>9</sup>

Five (5) of the multiparas were classified as habitual aborters, having experienced three or more abortions prior to coming under my purview. In these cases, the patients were placed on medication as early as the 3rd month. Of these 5 patients, 4 carried to term.

In the 13 primiparas, 11 or 84.6% carried to term (Table II). It is interesting to note in case no. 3 that following the first successful pregnancy when Lutrexin was used, the next pregnancy was not successful when Lutrexin was not administered. The third pregnancy, with the use of Lutrexin, had a successful outcome.

#### SUMMARY AND CONCLUSION

In a 10-year study of private patients, the uterine relaxing hormone, lututrin, has proved effective in 84.6% of 88 treated patients. Included were diabetics, RH factor problems and patients who had abruptio placentas. From these findings, it can be concluded that lututrin is successful in controlling abnormal uterine contractions.

A few positive results should be worth noting from this study. The medication used is not a panacea for all the ills of labor. It can be extremely useful in certain circumstances and the removal of this medication, although it has only a clinical background, will reduce the chances of the fetus of a premature labor to the time prior to lututrin of 43% to 45%. Where there is placental pathology, such as previa or abruptio, lututrin is not effective in diminishing the labors. However, in scanning the results, it is curious fact that some habitual aborters were aided in delivering a youngster in a viable time area.

Other medications have been employed by me, such as stilbestrol, aqueous corpus luteal extracts, vasodilan and delalutin, and the results were not comparable. All of these have their places in the medical armamentarium. It would be a grievous mistake to disallow the usage of lututrin, as it would be to bar all those mentioned. There are no fetal abnormalities and no material side effects with lututrin.

I have used lututrin over the past 13 years and still have the satisfying belief that this medication delivers a good child to a household at times rather than one plagued by prematurity, and certainly one who faces a future of uncertain, but inevitable improprieties.

TABLE I.—*The effect of using lutrexin in the treatment of 75 multiparas*

Number of Cases	Before Treatment with Lutrexin		Total Live Births	After Treatment with Lutrexin	
	Number of Previous Pregnancies	Total Pregnancies		Total Live Births	
24	1	24	11	18	
15	2	30	16	13	
10	3	30	18	10	
10	4	40	23	10	
11	5	55	28	9	
4	6	24	9	4	
1	7	7	4	1	
75		210	109	65	

Chi Square for Above Data, 26.6;  $P < .001$

TABLE II.—*A Resume of Thirteen (13) Primiparas Treated With Lutrexin*

*Patients*

*Case Number*

*Description of Case*

1. Ten years infertile—went into labor at six months—carried to term on Lutrexin.
2. Bicornuate uterus—four successful pregnancies on Lutrexin. (This patient has now carried four pregnancies to completion with Lutrexin.)
3. Bicornuate uterus—(first pregnancy carried on Lutrexin to term) (second pregnancy—no Lutrexin—delivered six weeks prematurely) (third pregnancy carried on Lutrexin to term)

TABLE II—Continued

## Patients

Case  
Number

## Description of Case

4. Sterility problem for six years. Placed on Lutrexin at 33 weeks. Delivered viable baby at 34 weeks.
5. Carried four weeks on Lutrexin—viable baby.
6. Placed on Lutrexin seven weeks prior to term—cervix dilated—sectioned one week before term.
7. Twin pregnancy—carried 39 weeks to viability on Lutrexin.
8. Early labor—placed on Lutrexin 38th week—viable baby at term.
9. Early labor—placed on Lutrexin 35th week—carried to term.
10. Ruptured membranes in second trimester—delivered at six months—dead fetus.
11. Ruptured membranes at 36 weeks—delivered dead fetus at term.
12. Went into labor at 24 weeks—carried to term on Lutrexin—viable baby.
13. Early labor at three months—delivered a viable infant at term after being placed on Lutrexin.

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The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *Statistical Evaluation in the Reduction of the Incidence of Prematurity*. (1968, unpublished)

(S) J. T. Majewski, M.D.  
JOSEPH T. MAJEWSKI, M.D.

Date March 5, 1970.

*The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea\**

(George H. Rezek, M.D., Cicero, Ill.)

The purpose of this paper is to report the favorable results secured in a series of clinical cases of dysmenorrhea with a new, nonsteroid, watersoluble uterine relaxing factor obtained from the corpus luteum.

In 1942<sup>1</sup> we published the results of a clinical study of the value of Lutein in 650 cases of threatened and habitual abortion and other obstetrical complications involving the necessity of inhibiting uterine contractions. The favorable results obtained were shown to be due to the effectiveness of this product in inhibiting uterine contractions, as demonstrated by the intrauterine bag method of Moir.<sup>2</sup> When 10 c.c. of aqueous Lutein were injected into a patient whose uterine contractions had been stimulated by 1 c.c. of Pituitrin, there was complete cessation of contractions within twenty-five minutes. It was apparent from our study that this inhibition of contraction was not due to the progesterone content of the solution, and we suspected the presence of a heretofore unidentified substance. We drew attention also to the imperative need of further investigation of corpus luteum derivatives to determine the reason for the results which we had secured.

At that time there was no satisfactory laboratory method of standardizing substances derived from the corpus luteum except in terms of progesterone, which, in our experience, does not produce uterine relaxation. An intensive investigation, undertaken to devise a laboratory method of assaying the potency of these substances in terms of such relaxation, culminated in the development of a new technique for the determination of their effect on uterine activity, which was published by Krantz, Bryant, and Carr<sup>3</sup> in 1950.

#### NEW UTERINE RELAXING FACTOR ASSAY

The new method of assay is based on the development and maintenance in the test animal of a uniform endocrine picture. This state was induced artificially in guinea pigs by injections of estrogenic material. One-tenth mg. of Diovoeylin injected

\*Presented at a meeting of the Chicago Gynecological Society, Jan. 16, 1953.

†Supplied by Hynson, Westcott & Dunning, Inc., Baltimore 1, Md.

subcutaneously into each animal daily for seven to twelve days before use caused proliferation of the uterus approximatey equal to that of a twenty-day pregnancy. In the conduct of the assay, the uterus is exposed through a midline abdominal incision, this organ then being attached to the writing lever of a kymograph. The jugular vein is also exposed for the purpose of making injections and the effect of such injections on uterine motility is observed by means of kymographic tracings.

A total of 26 different substances, including progesterone, were used with the idea of defining the specificity of the new factor in inhibiting uterine contractions. It was found that of these substances only the new uterine relaxing factor was effective. The test is, therefore, highly specific for this substance and is so extremely sensitive that 0.002 mg. produces definite relaxation.

The degree of relaxation of uterine contraction thus provides a direct method of assay of the potency of different samples of material obtained from the corpus luteum. Various methods of increasing this potency were devised and finally a highly active water-soluble nonsteroid substance was developed which inhibited uterine contractions when given by mouth as well as by injection.

A laboratory investigation reported by Hisaw and Frieden<sup>4</sup> at the Laurentian Conference on Hormones in Canada, September, 1952, establishes the fact that the uterine relaxing factor is a protein type of compound. It is interesting to note that still another ovarian substance was described by these investigators and their associates<sup>5</sup> at Harvard some years ago. This substance, which they have named relaxin, is closely related to the new uterine relaxing factor, but differs from it in that relaxin has the property of relaxing the symphysis pubis of the guinea pig. Further evidence that the two substances are not identical is provided by their electrophoresis curves.<sup>6</sup>

The effectiveness of the uterine relaxing factor in threatened and habitual abortion will be the subject of another paper.

### CLINICAL RESULTS

In view of the probable relationship between uterine contractions and dysmenorrhea it was decided to try the new potent substance orally in a series of clinical cases. This investigation was undertaken more than two years ago and to date a

total of 298 patients have been treated with highly satisfactory results. Seventy-two patients who responded well but who had also used a sedative were ruled out of this report.

For the purpose of clarity the clinical results will be divided into two series, the first treated by the original dosage schedule, and the second by a revised schedule.

#### FIRST SERIES

Seventy-three patients with a hyperplastic endometrium immediately before menstruation who used the new substance alone experienced relief from their cramps. Forty of these obtained excellent relief with 150 or 300 units every four hours. In this series the patients were observed for at least six periods and in some for as many as eleven periods. All were free from cramps and able to continue their daily routine, which they had been unable to do before use of the drug. Table I shows the number of periods observed in each of these cases.

TABLE I.—*Number of periods observed*

<i>Periods</i>	<i>Patients</i>
11 -----	4
10 -----	6
9 -----	15
8 -----	5
7 -----	5
6 -----	5

In another 20 cases the results can be described as good, in that patients were definitely better but did experience a few mild cramps. Each of these patients was observed for at least six periods. Fair results were obtained in 10 other cases. In this group the patients reported definite improvement but were still aware of menstrual cramps with some degree of pain. Only 3 stated that they had obtained no relief from the drug.

As a means of determining the elapsed time between the administration of the drug and relief of pain, 15 patients in the "excellent group" were asked to present themselves while having cramps and were given 450 units at once. Thirteen stated that within 15 minutes the cramps had almost completely disappeared. The other 2 had some improvement with the first dose and almost complete relief when an additional 300 units were given three hours later.



## REPRESENTATIVE CASE HISTORIES

C. R., aged 23 years, had had dysmenorrhea every month since she was 13 years old. She had had over a period of 8 years, as she stated it, "all types of endocrine therapy." A dilatation and curettement and finally a presacral sympathectomy were carried out without relief of her menstrual cramps. This patient experienced relief from the uterine relaxing substance if she was able to take it before menstrual nausea and vomiting set in. When the periods started at night and she began vomiting, she was unable to take tablets, but if the period began during the day and tablets were taken in time she received complete relief from her uterine cramps.

R. R., aged 28 years, had had dysmenorrhea since the birth of her second baby 4 years ago. Excellent results were experienced with 150 units every 4 hours.

K. D. aged 19 years, had had cramps since the onset of the menses at the age of 14 years. No previous therapy had been used, but she reported excellent results with 150 units every 4 hours.

M. P., aged 16 years, was a virgin and no endometrial biopsy was performed. She had had cramps since the onset of the menses at the age of 12, but received excellent results with 300 units every 4 hours. Rectal examination revealed no pelvic pathology.

A. B., aged 19 years, had had dysmenorrhea for the past 4 years. The menses started at the age of 13 and the first 2 years were pain free. There was no pelvic pathology. She received excellent results with 150 units every 4 hours.

R. H., aged 33 years, was a nullipara. The menses started at the age of 14 years; the first 10 years were without dysmenorrhea, but during the last 9 years, she has had severe dysmenorrhea. Pelvic examination revealed the patient to have bilateral salpingitis. Three hundred units of the drug every 4 hours gave excellent results in relieving cramps.

In the group with hypoplastic endometrium immediately premenstrually there were 10 patients; only 2 claimed some relief and 8 said they experienced no relief.

## SECOND SERIES

It was our impression at this time that, in general, patients responded more rapidly to the larger doses. In some instances

relief with dosages up to 450 units was not secured until the second, third, or fourth dose. We had seen no evidence whatsoever of untoward reaction and, in view of the fact that other investigators had used much larger doses experimentally, we decided to give an initial dose of 1,500 to 3,000 units. Patients in the second series received an average of 2,300 units initially. With this regimen we found that relief of pain was secured within approximately 15 minutes. Furthermore, in some cases only one dose was required for any given period.

Fifty-eight patients with normal endometrium were treated in this way and of these 40 experienced complete relief of pain within fifteen minutes. Of 10 other patients with hypoplastic endometrium 3 experienced relief with a dose of 3,000 units. It is apparent, therefore, that the larger dosage is more effective and that patients with a normal endometrium respond more readily and frequently than those with a hypoplastic endometrium. In this series patients were observed for at least three periods.

[Figures 1 and 2 omitted.]

A further observation in this series was that in a number of instances patients who suffered regularly from painful periods experienced no such symptoms for several periods following the use of 3,000 units of the uterine relaxing factor. The number of patients reporting relief for more than one period following a single large dose is not, however, sufficiently large to permit any definite conclusions.

#### LABORATORY CONFIRMATION

Since the guinea pig uterus relaxation test had been found to be highly specific for the new substance, it was decided, as an additional check on the absorption of the drug, to take blood samples from patients who had received it and to test them by the above method. As a control, samples of the patients' blood were also taken before administration of the drug. It was found that, although control samples produced no effect in inhibiting uterine contractions, specimens taken thirty minutes after administration produced a characteristic relaxation of the guinea pig uterus. This is illustrated in Figs. 1 and 2 which are reproductions of typical kymographic tracings secured before and after administration of the uterine relaxing factor in a total of 25 patients to date.

## SUMMARY

1. The highly favorable results in a series of 298 clinical cases of dysmenorrhea treated with a new potent uterine relaxing factor of the corpus luteum are described.

2. Complete relief was secured within fifteen minutes in approximately 70 per cent of patients with normal endometrium when treated with an initial dose of 3,000 units.

3. Response to the smaller initial dose used in the first series was not quite as satisfactory, demonstrating the need of a large first dose.

4. Patients with a hypoplastic endometrium appeared to respond less well.

5. No undesirable by-effects of any kind were noticed, although some patients were observed for as long as 11 periods.

6. All patients who responded were able to continue their daily routine, which they had previously been unable to do.

7. The suggested dosage for the new uterine relaxing factor is 1,500 to 3,000 units at the beginning of pain. In many cases no further drug is required for that period.

8. Absorption of the drug into the blood stream was confirmed by laboratory procedures.

## CONCLUSION

In our experience the new uterine relaxing factor described above is effective in the relief of menstrual pain.

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The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea*, which appeared in the American Journal of Obstetrics and Gynecology, Vol. 66, No. 2, p. 396, August, 1953.

GEORGE H. REZEK, M.D.

Date March 5, 1970.

*Lutrexin in the Treatment of Premature Labor*

(By G. H. Rezek, University of Illinois College of Medicine, Chicago, Ill.)

Since 1903, when Ludwig Frankel of Breslau showed that the removal of the corpus luteum in the pregnant rabbit caused it to abort, there has been a more or less constant search by many investigators to find a substance in the corpus luteum or ovary that could be used in the treatment of habitual and threatened abortion and premature labor. Since the paper by Krohn *et al.*,<sup>1</sup> there have been many papers that have shown that various extracts of the corpus luteum are of value in the treatment of threatened abortion and premature labor. In 1942 Falls *et al.*<sup>2</sup> showed relatively good results in over 600 cases with an injectable corpus luteum extract. In 1950 Krantz *et al.*<sup>3</sup> showed that an aqueous extract of the sow corpus luteum had the ability to diminish uterine tone and abolish contractions of the guinea pig uterus in situ. I<sup>4</sup> used the same material to determine its effectiveness in the treatment of dysmenorrhea. Jones and Smith<sup>5</sup> also used the substance in the treatment of dysmenorrhea. Majewski and Jennings (6a), (6b) continued the work with this substance in the treatment of clinically diagnosed cases of premature labor. It is my belief that threatened abortion differs from premature labor only in the length of gestation. Threatened abortion presents a problem in differentiating between a true threatened abortion and an incomplete abortion while, in premature labor, it is difficult to differentiate between premature labor and normal Braxton Hicks contractions. Because many different etiological factors may cause the premature emptying of the uterus, one can expect difficulty in finding one type of treatment to take care of all the factors. All the theories as to the mechanics of the onset of labor are

hypothetical. Some feel that the increasing size of the uterus may cause growing irritability and produce spontaneous labor. Other theories are concerned with the environment of the cervix and lower uterine segment of the uterus near term, the carbon dioxide content of the blood, and senility of the placenta. Lash and Lash<sup>7</sup> feel that the incompetent os is a factor in premature labor, and Trythall<sup>8</sup> has achieved 55 per cent good results with the use of Lutrexin in the treatment of the incompetent os. Others feel that psychic or physical trauma may be the trigger mechanism that produces premature labor. Since Snyder<sup>9</sup> has been able to prolong the duration of pregnancy in the rabbit by inducing ovulation near term, and since Heckel and Allen<sup>10</sup> have used progesterone to delay parturition of the rabbit, the hormonal initiation of labor probably is a good factor.

In this series of 54 cases of premature labor between 24 and 34 weeks' gestation treated with Lutrexin, the presence of at least 2 of the following 4 conditions was necessary for classification as premature labor: (1) regular uterine contractions causing definite discomfort to the patient; (2) at least 2-cm. cervical dilatation in a primipara and at least 3-cm. dilatation in a multipara; (3) some vaginal bleeding or a bloody show; and (4) rupture of the bag of water. Uterine contractions with progressive descent of the head but without cervical dilatation or bleeding were considered normal Braxton Hicks contractions and were not included in this series of 54 cases.

The treatment consisted of bed, rest plus 3000 units of Lutrexin\* orally every hour until the symptoms subsided, and then 3000 units 4 times a day for 2 days. After this the patient was permitted to be up, and received 1000 units 3 times a day until viability was reached (36 weeks). The patient was not awakened at night for therapy. In 36 of the 54 cases the patient was given a barbiturate at night for sleep; no sedation was used in the daytime except in 6 quite disturbed cases that required tranquilizers.

On the 54 cases, there were 14 failures; of these 14 failures, 2 fetuses survived—one weighed 3 lb. 14 oz., and one weighed 2 lb. 15 oz. In the 12 that did not survive the weight varied from 1 lb. 12 oz. to 3 lb. 15 oz. Two were stillborn. A case was classified as a failure if the patient continued to have pains and terminated the pregnancy. The 40 that were classified as suc-

\*Hynson, Westcott & Dunning, Inc., Baltimore, Md.

cesses continued with the pregnancy for at least an additional 28 days. In the group of failures, 4 were first seen with 4-cm. dilatation and ruptured membranes, and all terminated their pregnancies in less than 12 hours. In the salvage group of 40 cases, 5 had ruptured membranes, but with very little dilatation of the cervix (less than 2 cm). Thirteen patients of this series had been hospitalized previously as cases of threatened abortion between the tenth and sixteenth weeks of gestation. Four of the 54 cases proved to be cases of placenta praevia that began to bleed between 24 and 27 weeks. Diagnosis of placenta praevia was confirmed at the time of cesarean section between 36 and 38 weeks. One case of placenta praevia threatened to abort at 14 weeks and again at 19 weeks. In this series there were 30 primiparas and 24 multiparas. Of the 54 cases, 32 had lost at least 1 pregnancy and 2 had lost 3.

#### SUMMARY

In this series of 54 cases, premature labor was stopped in 40 cases (74 per cent) for at least 28 days. I feel that, by delaying delivery for 28 days or more, we have enabled many fetuses to survive that otherwise would have died because of prematurity.

It appears that the substance that inhibits uterine contractions and is of value in the treatment of premature labor, threatened abortion, and dysmenorrhea has not been completely isolated, but is found in Lutrexin in therapeutic amounts.

There were no untoward effects noted from this therapy.

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The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *Lutrexin in the Treatment of Premature Labor* which appeared in the *Annals of the New York Academy of Sciences*, Vol. 75, Art. 2, p. 995, January 1959.

GEORGE HENRY REZEK, M.D.

Date: March 5, 1970.

#### ARTICLES

### *The Use of Progestational Agents in Pregnancy\**

(Willard M. Allen, MD, St. Louis, Missouri)

*There are many approaches to the treatment of habitual abortion. This paper presents a logical method substantiated by a convincing clinical study.*

The advent of the newer progestational agents has raised again the question of the presumed value of progesterone and related compounds in complications of pregnancy, such as threatened abortion, habitual abortion and premature labor. The physician today is confronted with a decision as to which one of the many compounds should be used and with the question of safety as well as effectiveness. Some physicians are therapeutic nihilists, others are enthusiasts for hormone therapy, others for psychotherapy and still others for vitamin therapy. With such divergent methods of treating these conditions it seems evident that no uniformly satisfactory method has been reached.

There is little disagreement regarding the need for some method for preventing premature labor. Prematurity takes a dreadful toll among newborn infants. If the premature survives there is apt to be great expense in the raising of the premature in addition to the apprehension concerning the future health of the child. A whole specialty has been developed by the Pediatricians to care for these tiny newborns, yet precious little has been accomplished as yet to prevent the premature birth of babies, the majority of which are surely normal babies who would have had a much better chance for life had they been born at or near term.

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\* Presented at 61st Annual Meeting of the Wyoming State Medical Society, Sept. 1964. From the Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Mo.

The problem of early abortion is equally challenging although not quite so devastating to the family as premature labor. Habitual abortion, on the other hand, is a serious situation which creates many family problems.

Threatened abortion is an ever present problem to the physician who does obstetrics. Probably one pregnancy in ten results in abortion. Many of these are "blighted" and the abortion is Nature's method of ridding the patient of an abnormal fetus. Various explanations for the blighted pregnancy are given, such as late fertilization of the ovum, an inadequate progestational endometrium resulting in poor placentation, nutritional deficiencies, etc. The therapeutic nihilist insists that nothing should be done to discourage abortion because the fetus is abnormal anyway. However, I do not believe that we can take the view that a fetus which is abnormal at the time of abortion was necessarily abnormal from the time of conception or even from the time of implantation. One only has to recall the thalidomide tragedy to realize that supposedly safe drugs can have a catastrophic effect when given at a critical period in early pregnancy. Also we need to remind ourselves that excessive amounts of both estrogens and androgens, or certain vitamin deficiencies in early pregnancy in certain animals can destroy the pregnancy. Some of the abnormal fetuses which result in abortion may be man-made although not necessarily physician-induced.

The desirability of treatment of a threatened abortion is obviously open to some question. However, if one elects to treat such a patient a pelvic examination should surely be done. In many cases the uterus is smaller than expected. Such patients should not receive hormone therapy. We have seen numerous patients in which the abortion of an abnormal pregnancy has been delayed for weeks, or even months, by the use of progestational agents. On the other hand, if the uterus is soft and enlarged to the expected degree, the use of progestational agents may save the pregnancy. It is, of course, difficult to prove statistically that hormone therapy does save the pregnancy as there are many pregnancies in which bleeding and cramping occur yet the pregnancy proceeds normally with no therapy other than rest in bed. This fact makes it imperative that the



progestational agent be safe even though its effectiveness in threatened abortion can not be proved beyond question.

#### DISCOVERY OF PROGESTERONE

With this introduction, half philosophical, I will proceed to a brief discussion of progesterone and the newer progestational agents. The presumed effectiveness of progestational agents is based on the concept that a deficiency of progesterone may be responsible for abortion and premature labor. This concept did not originate from any knowledge which we have of hormonal deficiency in human pregnancy, but rather from extensive studies in animals which, in fact, led to the discovery of progesterone itself. These studies occurred so long ago that the current house-officers or young physicians know about them only by hearsay, yet they are not truly ancient, as I was an active participant in them. In many laboratory animals, removal of the ovaries during pregnancy results in abortion or premature delivery. The pregnancy terminates because of removal of the source of progesterone, namely the ovaries. Furthermore, the administration of progesterone (or in some animals, estrogen plus progesterone) permits the pregnancy to progress normally despite removal of the ovaries. However, for such animals to deliver, it was necessary to discontinue the progesterone, a fact which was further substantiated by the observation that parturition in normal animals could be delayed or even prevented entirely by the administration of progesterone.

It was, of course, easy to convert these extraordinarily valuable facts regarding animals to the concept that progesterone should be a cure-all for abortion and premature labor in the woman. Unfortunately, measurements of urinary pregnanediol and blood progesterone in human pregnancy give little or no firm indication of progesterone deficiency immediately prior to either term or premature labor. The fact still remains, however, that both pregnanediol and estrogen disappear from the urine within a few days following delivery of the fetus and placenta. Actual studies in human pregnancy, therefore, give little support to the concept. On the other hand, there is abundant evidence that the same hormones are being produced throughout human pregnancy as are produced in animals. These naturally

produced hormones must be essential to the successful completion of pregnancy yet their exact role or significance in parturition or premature labor remains obscure. This is rather disturbing when we realize that progesterone, estrogen and chorionic gonadotropin were discovered over 30 years ago, and their biological effects in animals were for the most part reasonably well clarified prior to 1940.

The use of progesterone and progestational agents in human pregnancy is, therefore, based on the unproved assumption that progesterone deficiency is responsible for threatened and habitual abortion, and premature labor. The information available from the medical literature does indicate that progestational agents are beneficial but I should emphasize that the results are not based on any clear-cut evidence of progesterone deficiency. There is no need, therefore, of using any laboratory test for pregnanediol as a requirement for therapy.

#### EVIDENCE OF USEFULNESS

I would like, now, to give you some of the evidence which substantiates progestational agents as useful drugs in the treatment of habitual abortion and premature labor. I will present first the results of my own experience on 20 private patients, all referred to me because of the problem. The most obvious fact is that these 20 women had experienced 80 pregnancies with only 10 living children prior to the pregnancy treated with the progestational agent. This proves beyond doubt that this group is made up of patients with some serious disorder leading to poor obstetrical performance. No obvious cause was responsible, no patient had hypertension or kidney disease, and only one patient was known to have a congenital malformation of the uterus (only two patients had the Shirodkar operation as an adjunct to hormone therapy). There may be some question as to the desirability of treating patients who have had only two consecutive losses prior to the treated pregnancy. In actual fact, there were only two patients in the group who had lost but two pregnancies prior to the treated pregnancy. One of these had lost two normal children at 5½ months from prematurity and the other patient had two abortions at 3½ months with normally developed fetuses (Table 1).

TABLE 1.—*Fetal salvage in cases with two consecutive abortions immediately preceding pregnancy treated with progestational agent*

	Treated Pregnancy	All Previous Pregnancies
Total No.....	20	80
Full term, survived.....	14	8
Premature, survived.....	4	2
Premature, died.....	0	19
Missed Abortion.....	1	4
Early Abortion.....	1	47
Success Rate.....	18/20 (90%)	10/80 (12.5%)

The next obvious fact is that in the first pregnancy treated with the progestational agent, 18 living children survived, four of which were born prematurely. In the great majority of these pregnancies the progestational agent was begun as soon as the pregnancy was definitely established and usually about two weeks after the period was missed. These cases were not actually all treated with the same hormone. Two cases were given 50 mg. progesterone i.m. daily, two cases received 100 mg. progesterone sublingually daily, one case received Pranone, and 15 cases received Delalutin, 125–250 mg. two or more times weekly. There was one early abortion in the 20 pregnancies. This is about the expected incidence. The premature rate of 20 per cent is somewhat higher than expected. Actually, the rate is virtually the same as in the previous untreated pregnancies in the group. However, in the previous pregnancies only 2 or 21 prematures survived, whereas all 4 of the prematures in the treated pregnancies were sufficiently mature to survive. These results, surely, indicate that the treated pregnancy gave a measure of family happiness not experienced from the previous pregnancies.

According to Malpas, after one abortion the success rate in the next pregnancy is 78 per cent, after two consecutive abortions, 62 per cent, after three consecutive abortions, 27 per cent, and after four the chance of success in the next pregnancy is reduced to 8 per cent. These figures surely indicate that repeated abortions, especially after three consecutive abortions, reduces the probability of a successful pregnancy to a very discouraging level. Correspondingly, these figures lend considerable credence

to the belief that therapy is beneficial when a high percentage of pregnancies are saved.

In this series the histories were sufficiently reliable to tabulate the success rate in relation to the order of the pregnancy. In the very first pregnancy these 20 women had 6 living children. At the end of the first 40 pregnancies (i.e. 2 pregnancies per subject) there were only 7 living children, and at the end of the first 55 pregnancies (2 or 3 per subject) there were only 10 living children. These patients, therefore, showed no tendency to secure better fetal salvage as they had more pregnancies. The spontaneous "cure-rate" in this group, therefore, was not apparent (Table 2).

TABLE 2.—*Fetal salvage prior to treated pregnancy, 20 cases*

Order of Pregnancy	1	2	3	4	5	6	7	8	9	Totals
Term Survivors.....	6	---	2	-----	-----	-----	-----	-----	-----	8
Premature Survivors.....	---	1	1	-----	-----	-----	-----	-----	-----	2
Premature Died.....	3	4	2	4	4	2	-----	-----	-----	19
Missed Abortions.....	---	1	2	-----	-----	1	-----	-----	-----	---
Abortions.....	11	14	8	7	2	1	2	1	1	47
Total.....	20	20	15	11	6	4	2	1	1	80
Percent Survival.....	30	5	20	0	0	0	0	0	0	12.5

The successful accomplishment of a pregnancy in patients with such a dismal history inevitably raises questions regarding the management of the next pregnancy. The patient obviously wants the next pregnancy managed in the same way as the successful pregnancy. The physician seldom has the opportunity to omit treatment and thereby secure a "control." This series is no exception. There were 24 pregnancies in this group after the first pregnancy treated with the progestational agent. In 18 of these the progestational agent was used. There were 16 term or near term normal children born (success rate 89 percent). In the 6 untreated pregnancies, 4 normal living children were born and 2 pregnancies resulted in prematures that failed to survive (success rate 67 percent). While little significance can be given such small numbers, it would appear that the salvage rate in untreated pregnancies, even after the successful completion of one or more pregnancies with therapy, is perhaps below the expected (Table 3).

TABLE 3.—*Fetal salvage in pregnancies subsequent to first pregnancy treated with progestational agent*

	Treated	Untreated
Total No.....	18	6
Full term, survived.....	15	4
Premature, survived.....	1	-----
Premature, died.....	1	2
Early Abortion.....	1	-----
Success Rate.....	16/18(89%)	4/6(67%)

At this point I presume most of you have concluded that I have over-emphasized the good results in the small series of cases, but if you have, your conclusion is premature. There are other studies which are reliable and which are in agreement with my own. In 1957<sup>4</sup> Davis and Plotz reported their results in the treatment of 90 cases of habitual abortion with intramuscular progesterone. The fetal salvage in pregnancies prior to the treated pregnancy was 13.8 per cent and in the treated pregnancy 69.7 per cent. The next year Reifenstein compiled the results of treating 89 cases of habitual abortion with Delalutin. In his group of cases the salvage prior to the treated pregnancy was 13.4 per cent and in the treated pregnancy 70 per cent. Boschann<sup>5</sup> likewise has reported his results in 12 cases of habitual abortion (three consecutive abortions immediately preceding the treated pregnancy). The success rate prior to the treated pregnancy was 21 per cent and in the treated pregnancy 67 per cent. My own cases are in accord with these results.

I think it is quite proper to conclude that both progesterone and Delalutin are effective agents in the treatment of habitual abortion. Also, it is well known from these studies that the female infants were not masculinized at birth despite large doses of either progesterone or Delalutin beginning very early in pregnancy. It is proper, therefore, to also conclude that these hormones are safe.

There is a good deal of uncertainty regarding what type of study should be carried out in order to fully establish the validity of the results. In these studies the patient herself serves as the control; the results in the pregnancies prior to the treated pregnancy are compared with the results in the treated pregnancy. A supposedly better method of study which is popular

today would utilize the placebo method; one patient receives the hormone and the next patient the placebo, the investigator not knowing which patient received the placebo until the study is complete. This type of study is now so "sacred" that any other type is often not recognized as investigative. However, there are many clinical problems in which this type of study violates the rules of clinical morality as well as common sense. Let us consider some disease in which the risk of death is appreciable, lobar pneumonia, for example. No clinician could risk treating alternate cases with an antibiotic and a placebo. In such a study the risk of death while receiving the placebo might be as much as 25 per cent. In the study of habitual abortion the risk of death to the fetus in utero is between 80 to 90 per cent. It seems to me that one no longer has the right to use a placebo as a control because the data already available from the studies in which the patient serves as her own control indicate that the fetal losses are reduced from 80 or 90 per cent to 25 per cent or perhaps less.

The contrasting point of view has been eloquently presented by Goldzieber.<sup>6</sup> He rejects the idea that a patient can serve as her own control. He points out quite properly that the solicitous help of the physician may exert a beneficial effect and gives data to indicate that equally good results in habitual abortion have been reported from various types of therapy which could scarcely be called specific. Javert<sup>7</sup> is of the same opinion. These contrary opinions do not, of course, alter in any way the results which have been obtained and are here reported; the interpretation of the results may vary but the observations are facts.

I have presented these aspects of the problem to emphasize that I believe drugs should not be eliminated from the armamentarium of physicians because their effectiveness may not have been proved beyond all possibility of doubt. New drugs should be as safe as possible, but even safety of an effective drug can never be fully guaranteed. Safety and effectiveness are words like good and evil. Their meaning is always related to something such as the seriousness of the disease, the magnitude of the crime or the mores of society.

The objection of Goldzieber<sup>6</sup> to using the patient as her control may be partially met by a recently reported study by LeVine.<sup>8</sup> He has compared the effect of a placebo and Dela-

lutin in 30 cases of habitual abortion. One half of the patients received 250 mgm. of Delalutin twice weekly and the other half received a placebo injection. The success rate was 73 per cent in the patients receiving the hormone and 42 per cent in the controls.

The data I have presented to this point deal with the use of two compounds, progesterone and Delalutin. To be effective these compounds must be given by intramuscular injection. Delalutin is the caproate ester of 17-hydroxy-progesterone. So far as we know, this compound has all of the properties of natural progesterone. It has the distinct advantage of being much more soluble in sesame oil and is also somewhat more prolonged in action. This hormone has, therefore, replaced progesterone for use during pregnancy where large doses over a long period of time are necessary.

The advent of orally effective progestational agents has, of course, introduced a new approach to the problem. Enovid, Orthonovum, Norlutin, Dufaston, Norinyl, Provera, and Provest are all orally active progestational agents, each being able to produce a progestational endometrium in the woman. They are, therefore, potentially useful in theory at least. Enovid, Orthonovum, Norinyl and Provest all contain added estrogen. This estrogen is added to enhance their capacity to suppress ovulation. The added estrogen would not necessarily reduce their usefulness during pregnancy. These compounds are not utilized as a rule because they contain only small amounts of the progestational agent.

The effectiveness of Provera and Norlutin, orally active progestational agents, has not been as fully established, in my opinion, as has the effectiveness of Delalutin and progesterone. However, the data available suggest that some of these preparations may be useful. Literally thousands of cases of threatened abortion have received Provera and Depoprovera. As I mentioned earlier, it is difficult, if not impossible, to prove effectiveness beyond doubt in threatened abortion. No extensive series of habitual abortions has been reported with Provera. However, Berard<sup>2</sup> has recently reported his results in treatment of threatened abortion and habitual abortion. In his cases there were 11 who were habitual aborters. In the pregnancy treated with Provera (orally, 10-30 mgm. daily) 10 living

fetuses were delivered at or near term. This small series, therefore, tends to indicate that oral Provera may be as effective as intramuscular Delalutin or progesterone.

The differences of opinion regarding the effectiveness of progestational agents in human pregnancy are unlikely to be resolved in the near future. There is no simple way of inducing progesterone deficiency in the pregnant woman nor does Nature, herself, provide us with any disorders in which there is clear cut progesterone deficiency. The problem is infinitely more complicated in the woman than it is in the pregnant rabbit where progesterone deficiency can be deliberately induced by ovariectomy during pregnancy. In this animal, progesterone, Delalutin<sup>10</sup> and Provera<sup>11</sup> supplement perfectly for the deficiency of progesterone induced by ovariectomy but Norlutin<sup>1</sup> does not. Until methods are evolved which will diagnose progesterone deficiency before irreparable damage to the pregnancy has occurred clinical methods such as have been reported will have to suffice as evidence regarding their effectiveness.

#### SUMMARY

A series of 20 cases of habitual abortion treated with progesterone or Delalutin is reported. These 20 women experienced 80 pregnancies with only 10 living children (12.5 percent) before they entered the study. In the first treated pregnancy 18 children (90 percent) survived. These results are in accord with other series reported in the literature.

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#### OBSTETRICS AND GYNECOLOGY

### *Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases.*

The maintenance of the state of pregnancy as close to full term as possible is generally a prime consideration in the delivery of a viable baby. In my obstetrical practice, I have employed Lutrexin in the management of cases of premature labor, threatened abortion and habitual abortion for the past fifteen years and a review of my records of the last three years reveals about 86% success in the treatment of such cases. The following description of fifteen recent representative cases reveals the effectiveness of Lutrexin in the treatment of these allied conditions.

In six patients (No. 1, 3, 5, 6, 10 and 15), there were histories of miscarriage, premature deliveries and abortion prior to presentation at my office for care. In twelve earlier pregnancies, there were only two live births. With the use of Lutrexin in these patients, covering from one to four pregnancies, there were eleven live births and no deaths.

Five patients (No. 7, 8, 9, 12 and 14) did not have prior histories of miscarriages, abortions or prematurity when first seen. Most of these patients were generally characterized by cramps, but with the use of Lutrexin during all of their pregnancies, they delivered a total of eleven healthy babies over as little as one to as many as five pregnancies.

In the remaining four patients (#2, 4, 11 and 13), it is of interest to note that patient #2 delivered viable babies during her first and third pregnancies when Lutrexin was used, but had a miscarriage during the second pregnancy when the drug was not employed. Patient No. 4 showed one failure and one success with Lutrexin therapy. Patient No. 5 in five pregnancies delivered four viable and one dead baby. Patient No. 13, with the help of Lutrexin, delivered viable babies in three of her pregnancies: during her fourth pregnancy when this treatment was not administered, a spontaneous abortion occurred.

If the five patients (# 7, 8, 9, 12 and 14) who did not have any prior history of miscarriages, etc. are excluded (although my experience indicates that in many instances such cases when not treated with Lutrexin are less likely to deliver viable babies), then in the remaining ten cases when Lutrexin was not used, there were only four live births out of eighteen pregnancies; when Lutrexin was used, there were twenty-one live births out of twenty-three pregnancies. This difference is highly significant,  $P = .001$ .

To summarize, for over fifteen years I have found Lutrexin to be a most useful drug in the treatment of premature labor and threatened and habitual abortion, with a successful rate of about 86%. Side effects with Lutrexin have never been noted in studies or in my practice.

Sincerely,

(S) Fred B. Gray, M.D.  
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FBG:ch

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#### RESUME OF CASES TREATED BY LUTREXIN FOR PREMATURE LABOR, THREATENED ABORTIONS AND HABITUAL ABORTIONS

##### OBSTETRICS AND GYNECOLOGY

###### *Cases*

- 1 1. A 22 year old WF came to my office 5 months after she had a miscarriage at 6 weeks gestation. She was five weeks pregnant and cramping. I put her on Lutrexin at once and gave her progesterones IM and sedatives when the cramping was complicated with spotting. She had a normal fast delivery on August 15, 1968 at term.
- 2 2. This 22 year old WF was treated with Lutrexin and progesterones throughout her first pregnancy and had a normal delivery at 38 weeks gestation. I was out of town early in her second pregnancy. She did not receive any Lutrexin and had a miscarriage at six weeks gestation. Early in her third pregnancy she began cramping and spotting. She was given progesterones along with Lu-

Cases

trexin as long as the spotting continued and then carried along on Lutrexin only. She was delivered of a viable baby at 36 weeks gestation.

- 2 3. This girl came to me at the age of 27 after having 3 premature deliveries and two dead and one live baby. She was eight weeks pregnant when she came in and was cramping severely. She was placed on a Lutrexin schedule and was delivered of a viable baby at 8 months gestation.

Three years later she came in again with the same problem and was given the same treatment. She maintained her pregnancy for 39 weeks and was delivered of a healthy infant.

- 3 4. This 35 year old WF had two normal deliveries and one spontaneous abortion in Detroit. Five years later she came to me when she was twelve weeks pregnant. She was cramping and was put on the Lutrexin schedule along with bed rest. In spite of all efforts, she had a spontaneous abortion at 16 weeks gestation. Four months later she was pregnant again with the usual cramping. At four months gestation the fetal heart could not be heard and she had a prolapsed cord. She had a miscarriage and D & C. Two years later she was pregnant again and was given Lutrexin at once and continued throughout her pregnancy. She maintained this pregnancy for 39 weeks when a low cervical Caesarian section was done because of a transverse lie. The baby was healthy although there was a lot of meconium in the amniotic fluid.
- 2 5. This 35 year old WF had had an abortion at 4 months gestation in Oct. 1957, another miscarriage at 5 months gestation in August 1958 and another at 6 months gestation in December 1959. She came to me in June of 1965 at ten weeks gestation. She was immediately started on the Lutrexin regime and was delivered of a healthy baby at term. In October of 1967 she was placed on Lutrexin beginning in the eighth week of her pregnancy. She was delivered of a 7 pound 12½ ounce infant at term.
- 4 6. This young lady had two spontaneous abortions in her first pregnancies. In her subsequent four pregnancies she was placed on Lutrexin whenever she started cramping and kept on it until the cramping abated. She had four normal deliveries at term.

*Cases*

- 3 7. This patient was kept on Lutrexin throughout three pregnancies and was delivered of three healthy infants—two at term and one at 36 weeks gestation. Her membranes ruptured at 34 weeks when she was admitted to the hospital under careful surveillance and on Lutrexin.
- 1 8. This 28 year old WF had a relatively normal pregnancy until 34 weeks gestation when she began cramping. She was kept on Lutrexin and was delivered at term.
- 5 9. This young lady was a problem. She had cramps from 24 weeks on through 5 pregnancies which was complicated with marginal bleeding in the latter stages. Her pregnancies were maintained with the help of Lutrexin through 37 to 39 weeks and has 5 healthy youngsters.
- 1 10. This 23 year old lady had a normal delivery in 1962. On March 2, 1965 she had a sudden, spontaneous abortion at ten weeks gestation before she had any prenatal care. In July of 1965 she came to my office at 7 weeks gestation. At twelve weeks, she began cramping and was placed on Lutrexin and kept on it until delivery at 39 weeks. She is 22 weeks pregnant at the present time and to date she has had no problem but in the event she begins cramping, she will be put on the Lutrexin regime.
- 5 11. This young lady was and is also quite a problem. She has had five pregnancies and was on Lutrexin throughout each one. She had one full term delivery, 1 abortion at 5 months gestation and 3 premature deliveries. In three of her pregnancies the cramping was complicated with spotting which was controlled with progesterones. She has four healthy children which I firmly believe she would not have without the help of Lutrexin. Several times she was taking 2 Lutrexin tablets around the clock (every three hours). She said she did not need an alarm clock as when the medication started to wear off, the cramps would awaken her and would be relieved shortly after taking the Lutrexin.
- 1 12. This 30 year old white female began cramping at 16 weeks gestation and was given Lutrexin whenever she needed it until she delivered at 39 weeks.
- 3 13. This young lady had four pregnancies. She cramped throughout three of them and maintained her pregnan-

## Cases

cies for 38 weeks with the help of Lutrexin. Her fourth pregnancy was terminated at nine weeks by a spontaneous abortion. She had had no prenatal care. I was on vacation at the time.

- 1 14. This patient (age 27) had the complication of fibroids in the uterus when she became pregnant in early 1966. Her pregnancy followed a rocky course but with the help of Lutrexin and TLC she delivered at 38 weeks. She has a healthy boy. I performed a myomectomy on her in July of this year and we are hoping she will have future successful pregnancies.
- 1 15. This 24 year old WF had a miscarriage in Brighton in 1966 at 3 months gestation. She come to me in November 1967 at 6½ weeks gestation. She was already cramping and was started on Lutrexin. She leveled off and at 24 weeks she was taking it only when she started cramping. She was delivered of a viable infant at 38 weeks gestation.

I hope this resume will prove helpful to you.

Sincerely,

(S) Fred B. Gray, M.D.  
FRED B. GRAY, M.D.

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There are others—2 have twins at Butterworth Hospital now at 34 wks and she was 4 cm. dil. and contr. every 4 min. 45 sec. She had been on Lutrexin 2 qid. This was stepped up to 4 tabs every hour for 4 hrs. qid. and she is now 36 wks and her cervix is 2 cm. dil. I have x-rays of twins and hosp. confirmation of her treatment. The drug is routine at our hospital Butterworth.

(S) FBG

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### *Congenital Inadequacy of the Cervix as a Cause of Infertility*

(By S. W. Trythall, A.B., M.D., F.A.C.S., Detroit Michigan)

Factors responsible for successful termination of sterility cases studied in our office proved that patients falling in the relative infertility group had opened a channel of investigation leading to one of the specific causes of premature delivery in

the nullipara. This is the problem presented by the pathological lower uterine segment which we\* feel is of congenital origin.

From this review, the women in the above categories revealed pathology amenable to corrective treatment as follows:

First, by preventive therapy in thirteen prima gravidas with congenital inadequacy of the cervix. Early recognition made it possible to deliver 11 viable babies, thus avoiding neonatal death and a subsequent relative infertility.

Second, by preventive therapy in ten of the nineteen multi-gravidas who by history have congenital inadequacy. In these women investigation revealed that of their multiple early deliveries, the first one terminated prematurely without traumatic incidence to the cervix.

Third, by the use of the Lash technique or its modification in the tracheoplasty operation in fifteen of the above women.

The author encountered his first problem of the inadequate cervix twenty-two years ago and subsequently has had moderate success by conization of the internal os as Steinberg(16) reported at the International Fertility Association meetings in Naples in 1956. This procedure has been replaced by a modification of the Lash tracheoplasty technique.

From a survey of the literature and discussion by fellow practitioners of the causes and treatment of premature delivery, one suspects a lack of understanding of cervical inadequacy as one of the multiple and complex causes of early termination of pregnancy.

In a study of the modern textbooks, it was noted that Greenhill,(6) Eastman,(3) and Titus(18) were the only authors writing in detail of this important facet of the problem of premature labor.

Therefore, those of us working in obstetrics and infertility should be grateful to Dr. Abraham Lash for bringing into focus the problems of a group of relatively infertile women in whom no endocrine or wheat-germ routine would prevent an early delivery.

The definitive diagnosis and surgical correction of the incompetent cervical os was first correlated by him from the world literature which included the investigations of J. J. Fisher(5) personal communications with N. Sproat Heaney as quoted by

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Presented at the June, 1957 meeting of the American Obstetrical Society in New York.

Dr. Lash (7) and the studies of Palmer (11, 18) and Lacomme (11). Lash was distressed by the paucity of literature available during the past twenty-five years on this subject of second trimester abortion due to the incompetent cervix. The material was summarized in his two important papers, i.e., Lash and Lash, 1950 (7) and Rubovits, Cooperman, and Lash, 1953 (15).

The senior Dr. Lash, reporting to the International Infertility Association in Naples in May, 1956 (6) discussed the results of 44 tracheoplastics for this type of habitual abortion. He was able to follow thirty-four of these patients, showing viable pregnancies after surgery in twenty-nine (85 per cent).

However, in the original work of Lash and that of the few other men who report this problem, the traumatic factors of previous pregnancy, abortion, and cervical trauma were given as the predominant causes. A characteristic statement was, "In virtually all of our cases there was an antecedent history of trauma to the cervix (15)."

In our study of patients with inadequate cervixes, it was found that 32 per cent had had no previous pregnancy, abortion, or curettage. These cases without forewarning had lower uterine segments which became completely effaced and dilated early in the second trimester. We believe these are the women who have a congenital inadequacy of the cervix. When not detected, they will continue to contribute to the high premature death rate because of repeated early termination of pregnancies resulting in relatively infertile marriages. In our work we became aware that by frequent vaginal examinations we were able to detect the early effacement of the cervix. This occurs over an extended period of time in preparation of the uterus for premature delivery. This is in agreement with the recent publication of work done on the "Prevention of Premature Delivery" as reported by Dr. L. J. Stephens. (17) The definitive diagnosis must be made early and the proper treatment instituted if the pregnancy is to be carried at least to viability.

The importance of this problem of premature delivery in our state is emphasized by the following facts as reported by Dr. G. Corneliuson of the Michigan Department of Health: "(a) Prematurity is still the greatest cause of death in children; and (b) Prematurity ranks 7th as a cause of all deaths." (2)

Majewski and Jennings bring us abreast of the times in stating that between 6 and 7 per cent of the total United States births have been consistently premature. (9)



Great strides have been made in the past ten years in the reduction of neonatal death rates by the improved obstetrical care of the newborn. This has been accomplished largely by the work of Beck (1) and Potter (13, 14) in emphasizing the responsibility of the obstetrician for the first twenty-four hours of the infant's life.

By 1950, the year that terminated my ten-year study of perinatal morbidity and mortality at Crittenton General Hospital in Detroit, (19) it was possible to cut our rate by almost 50 per cent because of improved antenatal, intrapartum and postpartum care. At that time my attention was focused upon a discouragingly large group of the second trimester deaths of no known cause except prematurity.

Since then, the percentages in Michigan have remained almost static. In 1950, the neonatal death rate was 6.6 per 1,000. In 1955 it was 6.4. In 1955 there were 14,000 premature births or 7.3 per cent. This group accounted for 49 per cent of the fetal deaths. (2)

The author believes that early diagnosis of the inadequate lower uterine segment by all men practicing obstetrics would start a new trend which could change this figure to one which will begin to approach the irreducible minimum, as we are now experiencing in maternal mortality statistics.

The ideal method for the further reduction of the above figures as discussed by Potter (13) is a prophylaxis against the early delivery, thus circumventing the difficult task of caring for the immature infant.

In our office, one method used for preventing the premature delivery is the early diagnosis of the congenital inadequacy of the cervix. This has been facilitated by the fact that these women are infertility case studies and a complete investigation offered clues that they should be followed more closely than the routine pregnancies.

In the *prima gravida* group, it was noted that only one out of thirteen demonstrated abnormal hormone assays.

In the *multigravida* group, there were nineteen with relative infertility because of repeated premature terminations of pregnancy. Careful analysis of their histories including hospital records revealed no trauma to the lower uterine segment. When beginning treatment at our office, the women had a total of forty-seven conceptions with only a 20 per cent fetal salvage because of an apparent inadequate lower uterine segment. We,



therefore, consider them to be a badly neglected congenital type.

The following signs and symptoms were found in the majority of all cases:

1. The examination revealed a 5/6 to 1/6 corpus cervical ratio or a combination of hypogenital characteristics.

2. Ethiodal studies revealed that in a majority of the patients there is an abnormal uterine contour. The predominate variation presented is an arcuate type with a tendency to the bicornuate pattern. There is a consequent loss of the normal cervicocorpus angle which gives the cavity a truncated appearance.

Dr. Frederick Falls in a recent discussion of a paper on the cause of premature delivery stated that following a good many years of study of the configuration of the uterus he finds a rather large percentage of abnormality in habitual abortion problems. (4)

3. The Basal Body Temperature variations are minimal and nonconstant in the majority of these cases offering a clue to an approaching problem. No amount of hormones changed the temperature patterns. The patient took 450 milligrams of oral progesterone per day for 26 weeks.

4. Lower abdominal pressure, excessive painful uterine contractions, persistent dysuria, and rectal irritability were premonitory findings which could not be ignored if the diagnosis were to be made early.

5. Fetal movement becomes quiet from increased intra-uterine tension once effacement and dilatation occur.

Suspected patients are carefully instructed and asked to advise us when any one of the preceding conditions occurs. Speculum and vaginal examinations are mandatory in these women every five to seven days beginning in the second trimester. The definitive diagnosis is made on feeling and seeing complete effacement and at least 2 or 3 centimeters of cervical dilatation with the membrane presenting.

The inadequate cervix should be detected before the membrane is extruded through the os into a sphere because when this does occur, the total intra-uterine volume is diminished, the cervix contracts, and shearing of the placental bed may result in uterine bleeding before the rupture of the membranes.

This leads to a confusion in diagnosis of the true etiology causing the termination of pregnancy.

The membrane may present as a hemisphere as visualized in twenty of our cases of the inadequate cervix. With treatment relieving the hydrostatic pressure on the segment, the secundines will retract and the cervix close. Our experience has proved that this is a type of threatened abortion for which bed rest is one of the remedies.

Our first method of treatment then is that of preventive therapy in order to circumvent the early delivery:

1. Bed rest, high Trendelenburg, until the cervix closes
2. Bathroom and laxative privileges
3. Prophylaxis against intra-abdominal pressure
4. Carefully adjusted maternity corset
5. Lutrexin tablets, 4 STAT—three, two, one each hour until the contractions and uterine tension decrease in those patients with uterine irritability.
6. House calls
7. Termination of pregnancy by appointment to avoid a precipitous home delivery.

We have used Lutrexin since its introduction to the market.\* Patients have been instructed when and how to use this medication and to tabulate its effectiveness. Of the women given this preparation, 55 per cent report their ability to control the uterine contractions and symptoms with this drug.

After the cervix has closed, the membrane retracted, and the patient has a viable baby, she is given liberty commensurate with the adequacy of the cervix.

Following the above routine in the thirteen nulliparous women who had eighteen pregnancies with congenital inadequacy of the lower uterine segments, eleven infants (60 per cent) were carried to viability and survived. In seven patients the membranes ruptured before the twenty-sixth week resulting in fetal deaths.

In the multigravida group who had had a previous fetal salvage of 20 per cent, early visual diagnosis was made in ten cases. Of these babies, 80 per cent survived on the above conservative treatment.

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\*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland. Patients using Lutrexin were on individual prescription basis.

We realize that when bed rest might be necessary for as long as six months it may be extremely difficult for our patients. Therefore, we recommend tracheoplasty following delivery in all who have had a positive diagnosis by visual and digital examination of cervical inadequacy during pregnancy and confirmed by ethiodol studies.

We also recommend surgery for the women in whom the abnormality exists, proven by history and the Lash x-ray technique.

During the weeks that this paper was being completed, a woman in the above group who had successfully carried her last of five pregnancies to viability on conservative therapy, presented us with a second effacing dilating cervix at twenty-two weeks. Bed rest was impossible and, following a discussion with Dr. W. J. Mulligan,<sup>10</sup> it was decided to take a more positive approach to prevent the premature rupture of the membrane. Following his technique, a polyethylene (animal tested) 1/16 inch tubing was used as a purse string suture to close the cervix.

The writer believes that this definitive approach used in the early months of gestation in the women have bad histories of habitual abortion of this type would result in greater fetal salvage.

When indication for operation is not well defined, we prefer to observe the patient through a pregnancy before surgery.

We have used tracheoplasty in fifteen women. Six of these have not attempted to conceive. Seven have become pregnant and all have carried to term except one. This patient had a poor result from surgery and delivered a 3½ pound premature viable baby. Two who have conceived are in the third trimester with no foreseeable difficulty.

The purpose of this paper is to emphasize three important factors:

1. The possible fetal salvage by the early recognition of the congenital inadequate lower uterine segment as a definite entity causing prematurity and relative infertility.

2. To further stimulate all doctors practicing obstetrics to use the simple inexpensive diagnostic device of more vaginal examinations in the second trimester.

3. To prove there is a positive approach to avoiding infertility and fetal wastage by a direct attack upon the consistent 7 per cent premature birth rate which resulted in 1200 neonatal deaths in Michigan in 1955.<sup>2</sup>

## ACKNOWLEDGMENT

Gratitude is expressed to Drs. R. C. Jeremias and J. L. Gil-  
lard, my partners, who have spent many hours examining the  
patients cited in order to establish that congenital inadequacy  
of the cervix is a definite clinical entity as a cause for prema-  
ture and relative infertility.

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*Congenital Inadequacy of the Lower Uterine Segment  
as One Cause of Habitual Abortion*

(Sylvester W. Trythall, M.D., F.A.C.S., and Robert C.  
Jeremias, M.D.)

THE PURPOSE

IN our city this past year Drs. A. Lash (1) and R. Barter, (2) two of the foremost exponents of the incompetent cervix in our country, have discussed the inadequate cervix. Unequivocally they state that in their work congenital factors played a small role.

This paper is presented in order to report first, that in our office the inadequate lower uterine segment of congenital etiology is one of the most important causes of premature delivery, second to alert all those responsible for the care of pregnant women that the simple inexpensive diagnostic device of the weekly or bi-weekly vaginal examination after the twelfth week was our most important of all diagnostic devices. We are convinced that this routine has materially reduced our static 6 to 7(3) per cent premature birth rate and decreased our percentage of prematurity of no known cause.

In Michigan in 1956, (4) there were 14,000 premature births accounting for 49 percent of fetal deaths.

Eastman (5) in discussing, "The problems of the Evolution of Obstetrics", agrees that one half of neo-natal deaths are caused by prematurity as well as one-third of all problems of cerebral palsy. He states that in 60 per cent of these early deliveries the cause is unknown. He states that these births represent in essence some defect in one of the basic phenomena of reproduction, that of uterine contractility. Our experience with the majority of our congenitally inadequate uteri substantiate the idea that uterine irritability (6) is the most important part of a complex syndrome which must be identified early by the patient and the doctor if a threatened premature delivery is to be avoided.

Dr. Stallworthy (7) stressed at the I.F.A. Amsterdam meeting the practical fact that if we considered each pregnancy as a possible habitual abortion, more careful analysis for all the probable causal factors would result in fewer women being classed as chronic aborters.

We could find no standard definition in the literature, but from our work we propose that the primigravida be classified as having the "Congenital Inadequate Lower Uterine Segment" when digital and visual examination in the second trimester reveals effacement and 1 to 2 centimeters dilation of the cervix from painless uterine contractions. The patient must have had no previous cervical trauma more significant than an endometrial biopsy by a specialist. We recognize that this is an unsatisfactory method lacking controls, and it is the work of men like Bonilla (8) and Mann that will make a direct approach possible.

Dr. Mann's (9) group reporting on the "Sphincteric Function of the Uterine Isthmus" at the American Roentgen Society Meeting said that to date, 350 habitual aborters, 100 nonaborting controls have been studied. The X-ray findings coupled with clinical follow-up revealed that cervical incompetence can now be diagnosed in the nonpregnant state and that the sphincteric disability resides in the isthmus rather than the cervix.

#### THE MATERIAL

The case histories on which this investigation is based are provided by the past 3000 women of our private obstetrical and infertility practice. These are divided into 3 groups:

(a) The 27 primigravida patients who have demonstrated congenital inadequacy as has been defined.

(b) The 27 multigravida women under our care who by history, examination, and careful observation of a pregnancy have also indicated incompetency. In these women, complete investigation of the records revealed that the first of their multiple early deliveries terminated in the second trimester without pain or forewarning. These patients lead us to suspect they have been a badly neglected congenitally inadequate group.

(c) The 25 women who have had traumatic cervical incidents—this group is not included in this discussion.

#### METHODS USED IN THE DIAGNOSIS

(a) Careful, detailed evaluation of the genital tract with special attention to hypogenital characteristics: the cervix is measured with the uterine sound, and the internal os is cali-

brated with Hegar dilators. The short cervix was the most constant finding.

(b) Definite ethiodol studies in suspected cases, with standardized technique employed by the same operator. 84 per cent of the patients in today's report had Salpingograms. Dr. Kamm (10) reporting at the I. F. A. Amsterdam meeting stressed the need and importance of early X-ray study in abortion. Our ethiodol studies in these first two groups of women demonstrated four major intra-uterine contours:

(1) The majority were those with the predominant defect of an arcuate, long-truncated funnel type.

(2) The second in importance was the tricuspid.

(3) The third showed abnormally small cavities.

(4) Those with normal uterine contours were in the minority.

(c) Weekly or bi-weekly vaginal examination in all questionable and older primigravida after the twelfth week was the most definitive, and important diagnostic device. Our combined 40 years experience has taught us that pregnancy itself is the only reliable test for uterine adequacy.

(d) We alert the suspected patients to report to the office if they have an increased uterine irritability as indicated by:

1. An awareness of consistent rhythmical painless contractions.

2. Increasing dysuria.

3. Increasing rectal pressure or irritability.

4. Pulling sensation in the groin.

5. A feeling that suddenly the baby is very low and a sense of fullness in the pelvis.

#### TREATMENT

Conservative therapy is the most important and is used for all these irritable uteri until they are stabilized and the cervix closes. Experience has shown that it is poor technique to place a purse-string suture in the uterus which is already irritable.

We have learned that conservative therapy throughout the first pregnancy is best in:

(a) The patients of unknown uterine capacity.

(b) The women who by X-ray have demonstrated small uterine cavities.

We have discontinued tracheoplasty in this latter group.



## CONSERVATIVE THERAPY CONSISTS OF:

1. Bed rest in high Trendelenberg.
2. Bathroom and laxative privileges.
3. Carefully adjusted maternity garment.
4. Prophylaxis against intra-abdominal pressure.
5. Sufficient sedation to maintain patient at rest.
6. \*Lutrexin 4 stat repeat q 4 hrs. & p. r. n. until uterine contractions are controlled.

We have used the non-steroid extract of the pregnant sow's ovary, and 80 per cent of our patients with congenital lower uterine segment problems report their ability to control excessive uterine contractility and associated symptoms with this preparation. Our careful observation leads us to believe that this material has a quieting effect on the irritable uterine muscle. Massive doses have been (8) required in a few patients with no deleterious effects.

I would like to stress that we have not used surgery without a clinically proven inadequacy as required by our definition.

We have, however, altered our approach in the problems of the inadequate lower uterine segment. We reported surgery Palmer (11)-Lash (12) type as the treatment of choice for all proven inadequacy at the A. S. S. meeting in 1957. (13) Now in 1959 definitive therapy, consisting of either conservative treatment or the polyethylene circlage suture, is used during pregnancy as the individual case demands.

The women who by ethiodol study have long-truncated cavities are operated on by Dr. Jeremias in the second pregnancy when frequent examination reveals effacement and dilatation in the second trimester. He uses one or two .067" animal-tested polyethylene sutures which are placed to simulate the normal two-thirds to one-third ratio of the uterine contour. To date we have placed 18 such sutures. All of our nonabsorbent sutures are permanent but are available for cutting and removal if necessary. At present we have 5 pregnancies doing well following this therapy. One patient has had nine previous deliveries with non-viable infants. She is now at term.

From our experiences with 24 tracheoplasty operations in these two groups, we have decided to reserve this procedure for the traumatic cervix before a subsequent pregnancy. Because of poor healing we have encountered, the repair is now

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\*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland



reinforced by one or two permanent but removable .067" polyethylene Mulligan (15)-Shirodkar (16) type sutures which are placed just beneath the vaginal mucosa and are carried out and tied high in the posterior fornix.

### OUR RESULTS

In the congenital group, 27 patients have had 55 pregnancies; 33 babies survived. *Conservative therapy* was responsible for success in 77.4 per cent. Tracheoplasty contributed 9.7 per cent. Polyethylene circlage, 12.9 per cent.

Before treatment in the second or suspected congenital patients, 27 women had 73 pregnancies; 10 infants or 13.7 per cent survived.

During the interval these patients have been under our care, they have had an additional 32 conceptions. 23 babies or 71.9 per cent were viable following therapy which involved 52 per cent conservative treatment and 48 per cent surgical. The surgery involved 22 per cent polyethylene sutures and 26 per cent modified Palmer-Lash trachelorrhaphy.

### SUMMARY

1. We have endeavored to establish by direct or indirect methods a classification which would differentiate the cases of congenital uterine inadequacy from those of traumatic origin, both of which are responsible for premature delivery. The use of this classification in our practice has more definitely selected the patients to be subjected to surgery.
2. By employing our removable polyethylene purse-string suture, we are not committed to terminate the pregnancy by hysterotomy as are those using other synthetic mesh material as reported by Barter (16).
3. We feel that by urging all practitioners to employ the simple, inexpensive diagnostic device of frequent vaginal examination during the second trimester, the syndrome of uterine irritability and of the inadequate cervix will be recognized early enough to institute definitive therapy and thus cut down on the consistent 7 per cent (17) premature delivery rate in our country.
4. Our experience with medical treatment of the uterus with excessive irritability and congenital inadequacy would indicate that all practitioners without available hospital and surgical

privileges could expect reasonable success on conservative therapy.

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### *The Action of Aqueous Corpus Luteum Extract Upon Uterine Activity*

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The activity of aqueous extracts of corpus luteum on the uterus has been the subject of many investigations. Most of these investigations have involved the use of excised muscle or physiologically altered animals. Either ovariectomy or exposure of the uterus through the abdominal wall in such a manner as to permit insertion of a balloon, or sections of the uterus placed in a water bath are typical of these alterations. The

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physiological picture in either of the foregoing methods does not simulate the normal physiological picture as does the method herein described. The excised muscle test proved to be entirely nonspecific when used by us in the early part of this investigation. Twenty-six substances were tested and the excised uterus from pregnant mice was used in the water bath. Among the substances studied were those found in the aqueous corpus luteum preparation, or materials which were used in the manufacturing process of aqueous corpus luteum. Other unrelated compounds were tested in order to gain a broad view of the specificity of the reaction of the uterine section in the water bath.

The observation of Riley that chloretone relaxes the excised uterus was confirmed, but 15 of the 26 other substances studied by us also caused similar relaxation. Acids of the acetic and butyric type gave marked relaxation although sulfuric acid showed no effect. Boric acid caused a tension. The variation of  $pH$  caused a change in uterine effect. Atropine sulfate 0.5 per cent caused tension, while procaine hydrochloride 1 per cent produced no effect. Progesterone saturated aqueous solution caused a diminution of activity but no marked relaxation. Tri-cresol and tween 80 were among those substances eliciting relaxation of the muscle. The aqueous corpus luteum preparations studied gave a wide variation of effects from complete relaxation to marked tension of the muscle by simply manipulating the  $pH$  of the solutions.

Recently Riley showed that commercial samples of corpus luteum were capable of reducing the activity of the rabbit's uterus in vitro and in vivo. He demonstrated further that the relaxant action was presumably due to the 0.25 to 0.5 per cent of chlorobutanol present in the extracts as a preservative. Some aqueous corpus luteum preparations which were devoid of the preservative were reported by this investigator to be without relaxant action on the uterus. In addition, as mentioned above, Riley showed that solutions of chlorobutanol of the foregoing concentrations were capable of producing diminution of the activity of isolated uterine strip. In the light of these observations, it was suggested that the activity of aqueous extracts of corpus luteum owe their relaxant action to the presence of chlorobutanol "rather than to some heretofore unrecognized property of the corpus luteum."

As it was found that the excised section test was so unreliable, in the present investigation animal tests with the uterus intact were used. After many experiments on mice, rats, rabbits, and guinea pigs, an *in vivo* method has been designed whereby the relaxant action of aqueous corpus luteum can be positively demonstrated on the uterus *in situ*. This phenomenon of relaxation was observed during a series of experiments with guinea pigs, while investigation was made of the suggested reversal of adrenalin activity by the aqueous corpus luteum preparations (3). A definite relaxation of tonus and decrease in amplitude of contractions of the uterus were apparent after a single intravenous injection of aqueous corpus luteum. In many cases it was found that the activity of the uterus ceased completely for several minutes.

The present method of assay is based on the creation and maintenance in the test animal of a uniform endocrine picture. It is, unfortunately, not practical to use naturally pregnant animals because of uncertainty as to the stage of pregnancy. As a consequence, it was necessary to produce artificially a uniform state of uterine activity in the test animal by the use of estrogenic injections. The injection of 0.1 milligram of diovo-cylin per animal subcutaneously 7 to 12 days before use caused proliferation of the uterus, in size, equal to approximately that of a 20 day pregnancy. The guinea pig's uterus so prepared exhibited in most cases a regular pattern of activity when attached to the kymograph (Fig. I), as described here.

The test animals used were young virgin guinea pigs, weighing about 250 to 300 grams at the time the primer injection of estrone was given, and in no instance were castrates used. They gain weight during the 7 to 12 day period before the test and usually weigh about 350 grams at the time of the test. Guinea pigs at this weight are approaching sexual maturity. A number of pigs failed to demonstrate a normal uterine activity, and this lack of such activity was much more evident in the animals weighing 400 grams or over at the time of the test. Any animal failing to give a regular pattern of uterine activity for a 10 to 15 minute control period was discarded. It is important that the temperature of the saline spray remain fairly constant because temperature variation definitely affects the uterine activity. Young female rabbits were also used in this test method and also responded to the aqueous corpus luteum.

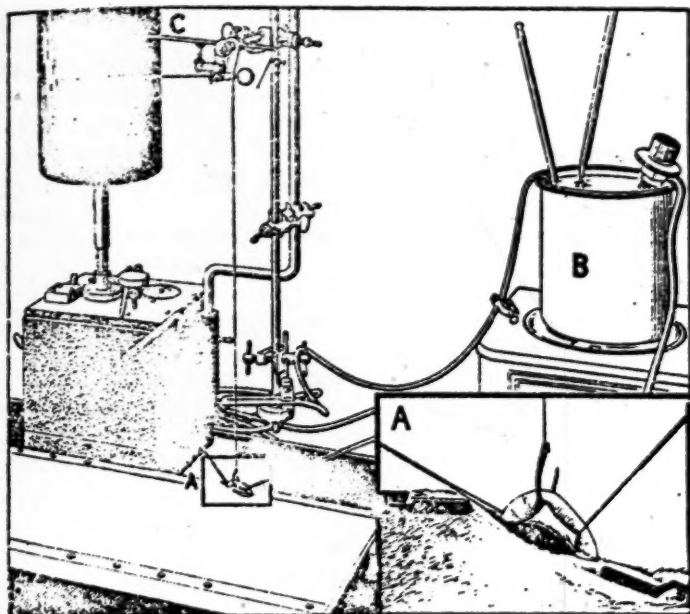


Fig. 1. Drawing showing apparatus and technique of making tracings of activity of uterus. The animal is placed on the table at lower left of drawing, and as shown in Inset A, the uterus is exteriorized and the muscle is attached to the writing lever.

The primed guinea pig is anesthetized by the injection intraperitoneally of 50 per cent urethane, approximately 1 cubic centimeter per animal. The uterus is exteriorized through a midline abdominal incision, and the muscle is attached to the writing lever as shown in Figure 1. A length of the uterus on either side of the half-curved needle, used to attach the uterus, was supported by loosely fitting cords so as to lift the muscle free of the other abdominal movements. Throughout the experiment the uterus was kept moist and maintained at body temperature by a warm saline solution spray. The jugular vein was exposed for purpose of injections, and all test injections were made intravenously throughout these experiments. The constancy and reliability of this method have been proved by the number of tests (61) done in this series.

## SUBSTANCES STUDIED\*

1. The first substance injected was a commercial aqueous lutein solution 2 cubic centimeters per kilogram, containing no chlorobutanol. Forty injections were made into 17 guinea pigs. Invariably a diminution in uterine activity was experienced. A typical tracing is shown in Figure 2. The rabbit's uterus responded in a similar manner (2 animals).

2. Solutions of chlorobutanol were injected (2 c.c. per kgm. of a 0.25 per cent solution). Twelve injections were made into 4 pigs. No diminution of the activity of the uterus was elicited by the substance upon intravenous injection. A typical tracing is shown in Figure 3.

3. Commercial aqueous extracts of corpus luteum identical with No. 1, containing 0.25 per cent of chlorobutanol, were injected. Nine injections were made into 3 guinea pigs. In no instance did the presence of chlorobutanol enhance the activity of corpus luteum extract upon the uterus. A comparison is shown in Figure 4.

One uterine horn of the animal represented by Figure 3 was extirpated and studied as a smooth muscle preparation *in vitro*. Figure 5 shows it was relaxed by chlorobutanol similar to results obtained by Riley.

It becomes clear upon examination of the tracing in Figures 2, 3, 4, and 5 that aqueous corpus luteum extract contains an active principle which, when carried to the uterus via the circulation, causes a diminution in uterine activity and tonus. The work of Hisaw and his associates (1, 2) at Harvard is confirmed in the observed uterine relaxant activity. It is also evident that this systemic action is not dependent upon the presence of the preservative chlorobutanol as the older methods of testing might suggest. Furthermore it appears that chlorobutanol is incapable of enhancing the uterine relaxant action of corpus luteum extract, as shown by this technique.

In order to determine whether or not this characteristic uterine relaxant activity manifested by the corpus luteum extracts could be produced by progesterone, the following experiments were performed:

Progesterone (5 mgm. per c.c.) was dissolved in tween 80.5 per cent, and injected intravenously, following our described technique. No relaxing effect upon the uterus *in situ* was pro-

\*Figures 2, 3, 4 and 5 omitted.

duced. Progesterone in aqueous suspension 5 milligrams per cubic centimeter was also used and found to elicit no effect.

In order to determine whether or not the action of the corpus luteum preparation was specific or due to some nonspecific constituent extractable by the manufacturing process, a control experiment was carried out. Since the commercial corpus luteum preparation used in these experiments was an extract of the sow's ovaries, a portion of the fresh intestine of the sow was subjected to the exact process used in preparing the commercial corpus luteum. This intestinal extract was tested on the guinea pig's uterus and found to elicit no relaxant activity.

#### CONCLUSIONS

1. Extracts of corpus luteum have been shown to produce relaxation of the uterus of the guinea pig and rabbit (previously primed with estrone) *in situ*, upon intravenous injection.
2. This action is not due to the presence of the preservative chlorobutanol.
3. A laboratory method has been perfected for demonstrating the relaxant activity of aqueous corpus luteum in the living animal.

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### *The Effects of Ovarian Extracts Upon Activity of the Guinea Pig Uterus in Situ*

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The presence of a substance in aqueous extracts of sow corpora lutea which possesses the ability to diminish the tone and abolish spontaneous contractions of the guinea pig uterus *in situ* was demonstrated by Krantz, Bryant and Carr (1950).

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Tests of a total of 26 samples of biological material and pharmacologically active substances, including epinephrine, acetylcholine, tyramine, chlorobutanol, and cobra venom, indicate that the response is highly specific for luteal extracts. The object of the present paper is to describe some of the chemical properties of the active substance (which we have termed 'uterine relaxing factor' (URF)), and to compare its properties and distribution with known ovarian hormones.

*Experimental.*—The bioassay of URF requires a test animal with a uniform, reproducible state of uterine activity. Uteri of pregnant guinea pigs, while suitable in some respects, were unreliable because of uncertainty as to the stage of pregnancy. A uniform motility may be produced by the administration of estrogen, and, in the experiments reported here, 0.10 mgm. *a*-estradiol propionate (Ciba) was injected daily into guinea pigs for seven to twelve days prior to the assay. This treatment causes growth of the uterus approximately comparable to that observed on the twentieth day of normal pregnancy. The animals found to be most satisfactory were young virgin females, weighing 300–350 gm. at the first priming injection. When used for assay 7–12 days later the animals were of early sexual maturity and weighed 350–400 gm. Such animals exhibit a regular pattern of activity when the uterus is exposed under urethane anesthesia. Animals failing to display regular patterns for a control period of 10–15 min. were discarded. The method of exposing the uterus and recording motility has been described elsewhere (Krantz, Bryant and Carr, 1950).

The unit of URF activity was arbitrarily established as the minimal amount which, when injected intravenously into the estrogen-treated guinea pig, effects a 90 per cent reduction in the height of spontaneous contractions for a period of at least ten minutes. Each sample tested was assayed at a minimum of three levels, the ratios of which were usually 1.0:0.75:0.56; the actual amounts selected were such that the three levels tested bridged the unit response as defined above. Three animals were used for each dose level. Estimates of relative URF content, therefore, are considered to be reliable to within  $\pm 50$  per cent.

Most of the URF preparations used in this study were made by dilute HCl extraction of dried, methanol extracted, unselected sows' ovaries. The filtered extract was brought to pH



6.5 and inactive material removed by filtration. The active fraction is contained in the precipitate, contaminated with relatively large quantities of ammonium sulfate and inactive protein. The former is removed by dialysis.

Relaxin was prepared from the ovaries of pregnant sows by the method of Frieden and Hisaw (1950). Pregnant rabbit serum was concentrated by the method of Albert and Money (1946). Relaxin assays were performed on groups of eight to ten guinea pigs according to the technique described previously (Frieden and Hisaw, 1950). Each preparation was assayed at three or more serial dilutions, chosen to correspond to the injection of from 0.5 to 2.0 guinea pig units (GPU). The reliability of estimates of relaxin content thus approximates that of most serial dilution assays ( $\pm 100$  per cent).

*Results. Chemical properties of URF.*—The substance in ovarian extracts which is responsible for uterine relaxation appears to be very stable. Exposure of URF solutions to 100°C. for five minutes results in but slight diminution of activity; solutions kept at 40°C. for two years likewise showed negligible losses. Most of the activity is retained following twelve-hour dialysis against running tap water.

The effects of reducing agents and proteolytic enzymes are indicated in table 1. Both trypsin and pepsin readily inactivate URF, as do cysteine, glutathione, sodium thioglycollate, BAL, ascorbic acid, and sodium bisulfite.

TABLE 1.—*Effects of reducing agents and enzymes upon URF preparations*

Reagent	Concentration (mgm./ml.)	pH	Reaction time (hr.)	Percent in activation
Cysteine.....	1	5.9	1	100
Glutathione.....	21	7.4	1	75
Sodium thioglycollate.....	8	7.7	20	100
Ascorbic acid.....	13	7.6	20	95
BAL (dimercaptopropanol).....	8	7.7	20	75
Sodium bisulfite.....	5	6.8	10	50
Trypsin.....	2	7.7	24 at 37°C.	100
Pepsin.....	2	1.5	24 at 37°C.	100

Final concentration of URF = 1.0 mgm./ml.

Unless otherwise indicated, mixtures were allowed to react at room temperature (25°C).

*URF and relaxin.*—It seems clear, from a consideration of the method of preparation and the properties of active extracts, that the phenomenon of uterine relaxation is not referable to the action of an ovarian steroid. Explicit elimination of the possibility that contamination with progesterone was responsible for the observed effect was afforded by experiments in which the injection of as much as 50 mgm. of this compound was shown to be without effect. On the other hand, the properties described above suggest that the active agent is probably protein- or peptide-like in nature. Since the only other non-steroidal physiologically active agent which has so far been isolated from ovarian tissues, namely relaxin, also appears to be a protein (Frieden, 1951a), it was of obvious interest to compare the properties of URF with those of relaxin. The chemical properties of URF parallel, with considerable fidelity, those of relaxin. Like the former, the latter is a heat-stable, slowly dialyzable substance, sensitive to proteolytic enzymes and a variety of reducing agents (Frieden, 1951a, b).<sup>2</sup>

Assays of URF activity were performed on a total of eight relaxin preparations, ranging in specific activity from 5 to 450 GPU per milligram. It may be seen (table 2) that all of these preparations possess the ability to diminish the motility of the uterus under the conditions of the URF assay. It further may be noted that preparations of high relaxin content (52-15, 66-4, 78-19) were found to be the most active with respect to URF content. However, the ratios of the two activities varied from 1:1 (preparations 79-1) to 1:8 (preparation 50-1).

Six URF preparations were tested for relaxin content (table 3); in but one instance was the ratio of relaxin to URF activity as high as 1:2, and in most instances the ratio was considerably smaller. Together, the data of tables 2 and 3 indicate that the ratio of relaxin to URF activity may vary over a twenty-fold range. While uncertainties in both assay methods may contribute to this variation, the wide divergence of relative potencies cannot be explained entirely on this basis.

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<sup>2</sup> Ascorbic acid appears to cause rather more inactivation of URF than of relaxin, while the opposite seems to be true for the action of sodium bisulfite. Differences in reaction time, reagent concentration or pH may account for these discrepancies.

TABLE 2.—*Comparative assays of relaxin preparations*

Preparation No.	Relaxin content (GPU/mgm.)	URF content (units/mgm.)
46-1.....	15	35
50-1.....	5	40
52-14.....	150	250
52-15.....	100	200
52-16.....	25	150
66-4.....	450	1,000
77-19.....	300	500
79-1.....	70	70

TABLE 3.—*Comparative assays of URF preparations*

Preparation No.	Relaxin content (GPU/mgm.)	URF content (units/mgm.)
W.O. 31.....	1.0	3
R-70-1.....	3.0	6
R-11.....	.5	8
R-86-2.....	5.0	36
R-6A.....	<5.0	100
1212.....	20 (per ml.)	200 (per ml.)

Studies of the comparative electrophoretic behavior of URF and relaxin serve further to emphasize the similarity between the two substances. Although neither has been obtained in electrophoretically homogeneous form, assays of the various cell fractions following electrophoresis of URF and relaxin preparations indicate that both are anionic at pH 7.7 and cationic at pH 6.0, i.e., both isoelectric points lie between these limits. The assay data also indicate that, at both pHs, the relative rates of migration of the two substances are, within limits of assay error, the same.

The relaxin content of the sow ovary has been shown to increase markedly during pregnancy. Thus, while the ovary of the mature, non-pregnant sow contains less than 25 GPU of relaxin per gram, those collected late in pregnancy contain from 300-1000 GPU/gm. (Frieden and Hisaw, 1950). It has also been demonstrated that relaxin is present in high concentration

in the serum of pregnant rabbits after the 24th day of pregnancy, while none can be detected in the blood of non-pregnant females<sup>3</sup> or males (Abramowitz *et al.*, 1944). To define further the relationship between URF and relaxin, extracts of selected lots of sows' ovaries and of pregnant rabbit serum and of male rabbit serum were assayed for URF activity.

The results of these experiments indicated that there exists a significant correlation between the tissue distribution of URF and that of relaxin. Extracts of ovaries of immature sows contain barely detectable quantities of URF. Larger amounts may be found in ovaries from mature animals, containing functional corpora lutea,<sup>4</sup> while the most active extracts are obtained from ovaries of animals in which pregnancy is well advanced. Like relaxin, URF is found in the blood of pregnant rabbits, while the blood of male rabbits is inactive. The serum of pregnant women also contains URF, as does the urine of pregnant women and pregnant cows.

*Discussion.*—It is not yet possible, on the basis of the data so far obtained, to define precisely the relationship between URF and relaxin. While the persistence of URF activity in purified relaxin preparations may be no more than coincidental, our data best fit the hypothesis that at least two substances will induce uterine relaxation and that relaxin is one of these. The chemical similarity between the two substances, as well as the observation that relaxin-poor URF is also found in the ovary, and apparently particularly concentrated in those with functional corpora lutea, suggests that we are dealing with two related compounds, with relaxin activity being confined to one of them.

Relaxin, or a substance with similar physiological activity, is found in the blood of a number of species of animals during pregnancy. (Hisaw and Zarrow, 1950), although only in guinea pigs has its presence been correlated definitely with relaxation of the symphysis pubis. The physiological significance of relaxin in such species is, as yet, without satisfactory explanation. The observations reported here suggest the possibility that relaxin may be concerned in the changes in myometrial activity

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<sup>3</sup> Very small amounts of relaxin may appear in the blood of non-pregnant rabbits during pseudopregnancy.

<sup>4</sup> Some of these may have been in the very early stages of pregnancy.

associated with functional corpora lutea and pregnancy (see Reynolds, 1949). In early work on this problem, the suggestion was advanced (Robson and Illingworth, 1931; de Fremery, Luchs and Tausk, 1931, 1932) that the luteal factor responsible for inhibition of spontaneous myometrial activity was distinct from that responsible for progestational modification of the endometrium; this view fell into disfavor when it was later established that crystalline progesterone was capable of producing both effects (Allen and Reynolds, 1935; Robson, 1936). In view of the fact that progesterone is capable of inducing the formation of relaxin in tissues of the female reproductive tract (Hisaw and Zarrow, 1938; Zarrow, 1948), the possibility exists that the effects of progesterone are indirect, and mediated through relaxin.

#### SUMMARY

Studies of the chemical properties of a uterine relaxing factor (URF), obtained from aqueous extracts of sows' ovaries indicate that the active agent is non-dialyzable, stable to heat, and sensitive to the action of proteolytic enzymes and a variety of reducing agents. It is concluded that URF is a protein or polypeptide. URF activity is also displayed by both crude and purified relaxin preparations, and comparison of the occurrence of URF and relaxin in various tissues suggests a close relationship between the two substances.

The possible relationship of protein-like hormones of the reproductive tract to changes in uterine motility have been discussed.

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*Treatment of the Dysmenorrhea Symptom Complex,  
A Preliminary Report on the Efficacy of a Uterine  
"Relaxing Factor"*

(GEORGEANNA S. JONES, M.D., AND FRANK SMITH, M.D., BALTIMORE, Md.)

(From the Departments of Gynecology and Medicine, Johns Hopkins Hospital and University)

Dysmenorrhea is a symptom complex composed not only of menstrual cramps but generalized symptoms, backache, leg ache, headache, diarrhea, nausea and vomiting, and general malaise. There is a great difference of opinion as to the exact etiology of the syndrome. Most observers believe that both smooth-muscle contractions and vascular constriction are components. These are somehow related to the ovarian steroid pattern, as anovulatory menses are usually painless. Ancillary factors are also of prime importance, especially psychosomatic factors. These may be manifested as relatively mild tension states due to temporary work or living habits or may be much more serious immaturity problems. It is well recognized that it is important to control symptoms of dysmenorrhea as soon after the onset of the syndrome as possible, for it tends to become a habit pattern. The woman who has dysmenorrhea learns to look forward to her menses with dread which in itself, by creating additional tension, aggravates the condition.

There are many types of therapy available. Current concepts have been nicely summarized by Miller and Behrman.<sup>(1)</sup> Simple bed rest and heat applied to the lower abdomen have always been at times effective, but for the working adult these are frequently impractical. Analgesic drugs are acceptable

therapy. However, drugs which are habit forming should certainly be avoided and all too frequently we find that only these are effective. Antispasmodics are also used and have their place in the therapeutic armamentarium. Approaching therapy from the standpoint of physiology we can prevent ovulation and thus prevent painful menses. Although theoretically this sounds quite logical, from a practical point of view it is not usually as successful as one might expect. In our experience it has been difficult to prevent ovulation repeatedly in the normally ovulating woman. Although one ovulation can be prevented rather readily, the second is often extremely difficult to suppress with either estrogens or androgens, unless the dosage given is excessive (Fig. 1). Estrogens in the required dose range are prone to disturb the menstrual rhythm and cause menorrhagia, while androgens may cause masculinization, neither of which is a desirable side effect. Operative procedures, other than the time-honored dilatation of the cervix, for this relatively minor condition are generally to be discouraged. Pre-sacral neurectomy is to be used only as a last resort and the results although frequently gratifying at the onset are often disappointing in the years following. (2)

With this relatively unsatisfactory armamentarium for the approach to the therapy of dysmenorrhea, a principle which would control the entire syndrome rather than single symptoms would therefore be most welcome. Hence, when an orally effective uterine relaxing factor (U.R.F.) was offered us for clinical testing on human beings it had enough points in its favor to warrant a trial.

In 1942, Falls and co-workers (3) reported the successful treatment of abortion with an aqueous extract of sow corpus luteum given intramuscularly. The action principle was therefore obviously not progesterone which is an alcohol-soluble, water-insoluble sterol. Krantz, Bryant, and Carr (4) in an effort to clarify the physiologically active principle, investigated the action of these aqueous extracts of sow corpora lutea on the isolated guinea pig uterus in situ and demonstrated the presence of a substance which possessed the ability to diminish the tone and abolish spontaneous muscular contraction. In the further identification of this substance, (5) it became apparent that it was closely related both chemically and in its biological activity



to a hormone described a number of years ago by Hisaw, (6) and designated as specific for the relaxation of the guinea pig symphysis. A chemical analysis by Felton and associates, (5) revealed that the uterine relaxing factor (U.R.F.) was, in addition to being water soluble, nondialyzable, heat stable, and destroyed by proteolytic enzymes and a variety of reducing agents. These properties seem to classify it as a protein or polypeptide.

Because of the ability of the hormone to produce uterine relaxation it seemed it might be of value in the treatment of dysmenorrhea. A report by Rezek (7) indicates that this is indeed possible. As an oral preparation is preferable to an intramuscular or intravenous one, experiments were designed to determine if there was any detectable relaxing activity in the blood serum after oral administration. Using the guinea pig as a test animal, it was found that 1 mg. of a typical sample of U.R.F. assayed 25 units per milligram, when tested by intravenous administration. The unit is "the minimal amount of substance which, when injected intravenously into the estrogenized virgin guinea pig, effects a 90 per cent reduction in the height of spontaneous contractions for a period of at least 10 minutes." (5) The same material assayed 1.25 units per milligram when given by stomach gavage. The assay of the serum of 9 women who received the hormone orally is seen in Table I. Although the blood serum of normally menstruating women not under treatment has shown consistently negative titers, the serum of pregnant women usually has shown a positive titer. These blood level experiments in both animals and human beings indicate that the preparation was absorbed orally. In testing the toxicity of the drug, as much as 10,000 units in a single dose was given to 10 men with no untoward results. (8) Two women under observation have also taken 10,000 units at one time and, although they were somewhat drowsy for several hours, no other effects were observed.



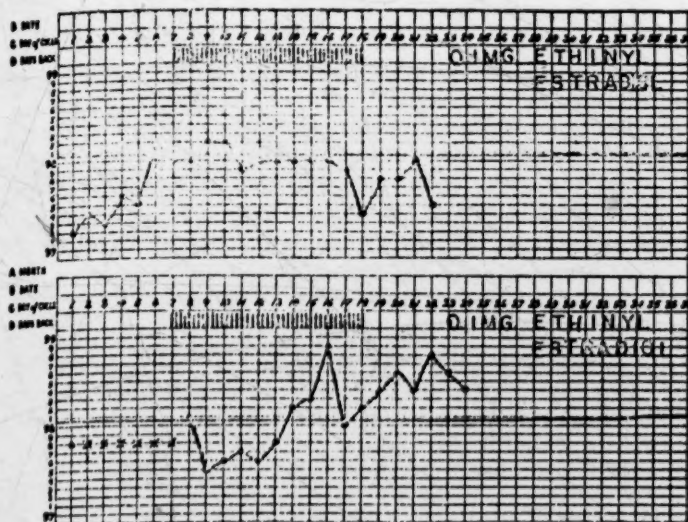


FIG. 1.—Basal temperature chart of patient receiving estrogen. Ovulation is suppressed in the first cycle but there is a rebound phenomenon and ovulation occurs in spite of continued estrogen therapy in the second cycle.

TABLE I.—Uterine relaxing factor in human serum after oral administration of lutrexin

Patients	Control period <sup>1</sup> URF/cc serum	Units lutrexin given	Test period URF/cc serum ½ hour after administration
1.....	None.....	1,500	1 unit.
2.....	None.....	1,500	None.
3.....	None.....	1,500	1 unit.
4.....	None.....	1,500	Trace.
5.....	None.....	1,500	½ unit.
6.....	None.....	3,000	1 unit.
7.....	None.....	3,000	None.
8.....	None.....	3,000	¾ unit.
9.....	None.....	3,000	1½ unit.

<sup>1</sup> Blood specimens drawn before Lutrexin was given.

## CLINICAL MATERIAL

In the present study 90 women who complained primarily of painful menstruation have been treated with tablets of U.R.F.\* They were all intelligent women, capable of evaluating the results, chiefly nurses, technicians, and aides on the hospital staff. No effort was made at the onset of treatment to differentiate the etiological factors of the dysmenorrhea. All had had some medication during previous periods of dysmenorrhea. None were told the nature of the new drug or what to expect in the way of amelioration of their symptoms except that the drug has been beneficial in tests elsewhere. Tablets were supplied in 500 and 1,000 units doses. Specific directions were given as to how and when they were to be taken. Only enough calculated for the current period and the ensuing one were given so that the patients would have to return for succeeding doses and to report on the results obtained.

## CLINICAL RESULTS

Of the 90 women in this series 47 had consistently good results with adequate dosage. Fourteen women had partial relief of symptoms, making a total of 61 patients with satisfactory response to therapy. Twenty-nine had no relief; 8 of these women were considered to be inadequately treated and were lost to follow-up examinations when attempts were made to locate them for re-treatment with increased dosage during a subsequent menstruation.

The 47 patients with good results included 24 women who received medication during more than one menstrual cycle. Ten patients were relieved of symptoms by an initial dose of 1,000 units and 1,000 units every 2 to 4 hours. One patient was relieved by an initial dose of 1,500 units, 3 required 2,000, and 29 required 3,000 units with an additional 1,000 units every 2 to 4 hours. One patient required 3,500 units. Seven women were unrelieved by 1,000 or 2,000 units but found 3,000 units were effective.

The group of 14 women who were classified as receiving fair results from medication were sufficiently relieved of symptoms to continue their duties but were still not completely free of discomfort. Two of these women took only 1,000 units at onset

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\* Lutrexin—Hynson, Wescott & Dunning, Inc.

of therapy and could not be persuaded to increase their dosage in an effort to obtain additional relief. Four have taken 1,000 units, two 2,000 units, and two 3,000 units during a single menstrual cycle. Three patients in this group have also had improved results with increased dosage.

Of the 29 women who were considered therapeutic failures, 10 were unavailable for follow-up study. Two of these 10 patients were adequately treated and the remaining 8 are to be considered inadequately treated as they received an initial dose of only 1,000 units with 1,000 units every 2 to 4 hours thereafter. Sixteen of the 19 remaining women who took medication two or more times without relief all received 3,000 units initially or during the second month of therapy. An effort was made to evaluate the pelvic findings and etiological factors contributing to the dysmenorrhea in this group of patients. Nine women were found to have normal pelvic structures, 3 had retroverted uteri and associated menorrhagia. Three had pelvic inflammatory disease, 1 had a myomatous uterus and menorrhagia, 2 had the Stein syndrome, 1 had dwarfism of the achondroplastic type with an infantile uterus, and 2 had severe vaginitis. One had menorrhagia associated with severe hyperthyroidism. However, although the patient is now in a euthyroid state on propylthiouracil medication, she still has excessive bleeding and dysmenorrhea. She obtained some relief if she was able to take her medication before the actual onset of severe cramps. But as she was often awakened from a sound sleep by menstrual cramps, this was frequently impossible. On occasions when it was possible to prevent ovulation with estrogens this patient had no pelvic discomfort. It is of interest that the dysmenorrhea of the achondroplastic dwarf was also relieved by prevention of ovulation. Seven patients refused pelvic examination. Six women in the group were thought to have rather severe anxiety neurosis with associated tension states in addition to other findings.

No side reactions were noted in any of the cases treated. One factor which contributed to the unwillingness to try larger doses was the number of pills to be ingested. In order to overcome this, future use of the drug will employ the tablets of larger unit content. It is also planned to run a concomitant control series by using placebos made up in exactly the same size and configuration. This necessitated the manufacturing of a special pill as the U.R.F. gives the tablet a brown-speckled appearance

which is not easily disguised. Like all therapy for dysmenorrhea, U.R.F. seemingly worked better when given early, ideally the day before menses started, and certainly before cramps became severe or nausea occurred.

#### SUMMARY

A uterine relaxant, a factor obtained from the corpus luteum of sow ovaries, has been isolated and the bio-assay standardized. It has been chemically classified as a protein or polypeptide. This substance is not destroyed in the stomach as the active principle appears in the blood serum within 30 minutes after oral administration in the human being. In a series of 90 women who complained of dysmenorrhea an initial dose of 1,000 to 3,000 units followed by 1,000 units every 2 to 4 hours was sufficient to control the symptoms of 61 women. Twenty-nine women had no results from therapy, but only 21 were considered adequately treated. Although the efficiency of medication for dysmenorrhea is notoriously difficult to evaluate, the fact that a number of women obtained no relief from small doses but adequate relief when larger amounts of U.R.F. were administered leads us to believe that the action is physiological rather than psychological. It seems from this preliminary survey that the uterine relaxing factor is of value in the treatment of dysmenorrhea as it relieves the entire symptom complex and has no sedative effect. It is apparently ineffective in those women with major psychosomatic difficulties or anatomically abnormal pelvises. Further studies are planned using larger doses as well as a control series making use of a placebo tablet similar in all respects to those containing U.R.F.

#### CONCLUSIONS

A new drug, capable of acting against dysmenorrhea and to be given orally, has been subjected to limited preliminary clinical tests. It shows enough satisfactory results to warrant its use. Studies will be continued to evaluate it further, especially to determine the optimal dosage.

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### *Lututrin: A New Drug for Relief of Dysmenorrhea*

(SCOTT S. JONES, M.D., TACOMA, WASHINGTON)

*Lututrin (LUTREXIN®) Protein-like substance extracted from ovarian tissue, which may be a new hormone, has given relief in 87 per cent of 40 cases.*

Dysmenorrhea is defined as painful menstruation, but actually is a symptom complex of abdominal cramps, backache, leg ache, headache, diarrhea, nausea and vomiting, and general malaise, occurring at the time of the menstrual period, and of varying degrees of severity.

There are as many or more kinds of treatment as there are symptoms. Physical and mental hygiene, exercise, heat, analgesics, hypnotics, smooth muscle relaxants, narcotics, endocrines, stem passaries, cervical dilatation, even presacral neurectomy. We have tried them all, with some success and many failures.

One can usually obtain a painless period by means of preventing ovulation with estrogens or androgens. But you cannot continue preventing ovulation month after month and you should not so upset the menstrual rhythm.

#### CHEMICAL AND MECHANICAL AIDS

In the field of drugs, I have had the best success with a combination of atropine, papaverine, aspirin, phenacetin and camphor monobromate. In some cases of severe cramps, I have had a measure of success with the flexible stem pessary. This is inserted in the office without anesthetic. It stimulates the uterus to react to the presence of a foreign body with strong contractions which, over a period of several weeks, result in increased vascularity of the myometrium. Not all cases respond and a certain amount of cervicitis is produced by the pessary.

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Read before meeting of Pacific Northwest Obstetrical and Gynecological Society at Victoria, B. C., May 18, 1955.

One hates to advise presacral neurectomy unless some other condition warrants operation. In spite of Cotte's report of excellent results, others have been unable to duplicate them. Even when relief is obtained, in some cases it has not been lasting. Hysterectomy is reserved for the older patient and one hesitates to remove a normal uterus for the symptom of pain alone.

### LUTUTRIN

Recently, I have been using a new drug called lututrin with excellent results in severe dysmenorrhea. This is a uterine relaxing factor obtained from the corpus luteum of sow ovaries and standardized for potency in terms of units of activity on the guinea pig uterus.\*

In 1942, it was found that uterine contractions stimulated by 1 cc. of pituitrin could be stopped within 25 minutes by giving 10 cc. of aqueous lutein. This was not due to progesterone, so the presence of some unidentified substance was suspected.

In 1950, Krantz, Bryant and Carr<sup>1</sup> used a new method of assay. A guinea pig was given estrogens for 12 days, the uterus was exposed and attached to a kymograph and the material to be tested was injected into the jugular vein.

Using this method, Rezek<sup>2</sup> found that a substance obtained from corpus luteum contained a uterine relaxing factor which was effective in inhibiting contractions of the uterus. It was so extremely potent that 0.002 mg. produced definite relaxation. This gives a direct method of assay of potency of the substance, which is a water soluble non-steroid. In 1952, Felton, Frieden and Bryant<sup>3</sup> established the fact that it is protein type of compound, or polypeptide. Years ago, Hisaw<sup>4</sup> had found another factor on ovarian substance, called relaxin, which has the

\* Marketed by Hynson, Westcott and Dunning under the trade name, Lutrexin.

<sup>1</sup> Krantz, J. C., Jr., Bryant, H. H., and Carr, C. J., Action of aqueous corpus luteum extract upon uterine activity, *Surg., Gynec. and Obst.* 90:372-375, (March) 1950.

<sup>2</sup> Rezek, G. H., Effect of a new potent uterine relaxing factor of the corpus luteum in treatment of dysmenorrhea, *Am. J. Obst. and Gynec.* 66:396-402, (Aug.) 1953.

<sup>3</sup> Felton, L. C., Frieden, E. H., and Bryant, H. H., Effects of ovarian extracts upon activity of guinea pig uterus in situ, *J. Pharmacol. and Exper. Therap.* 107:160-164, (Feb.) 1953.

<sup>4</sup> Hisaw, F. L., Experimental relaxation of the pubic ligament of the guinea pig, *Proc. Soc. Exper. Biol. and Med.* 23:661-663, (May) 1926.



property of relaxing the symphysis pubis of the guinea pig. The two substances are not identical.

The relaxing factor discovered by Rezek is not destroyed in the stomach. The active principle appears in the blood serum within 30 minutes after oral administration in the human.

Lutrexin comes in tablets of 1,000 unit strength. It appears to be non-toxic. Doses of 10,000 units have been given to both males and females without any untoward symptoms. The usual dose is 2,000 to 4,000 units when the cramps first begin, or even before they begin if the patient has any warning. One of three tablets may be given every 3 to 4 hours if necessary and as long as needed to keep the patient free of cramps. At first, I had a tendency to give too small a dose but I do not hesitate to give 4 tablets as the first dose now and in so doing have had much better results.

#### CLINICAL TRIAL

My associate and I have now treated approximately 40 cases of severe dysmenorrhea with lututrin. These were cases without other demonstrable disease. Results were classified as excellent when all symptoms were relieved, good when cramps were much abated and the patient was able to go about her work, fair when there was slight relief only, and poor when no relief was obtained. Using this classification, we had 23 or 57.5 percent excellent, 12 or 30 percent good, 2 fair and 3 poor. One said it made her feel worse. Thus, it can be seen that 87.5 percent of cases were greatly benefited. This is better than results I have had with any other type of treatment.

Jones and Smith<sup>5</sup> have reported a series of 90 women with pain controlled in 61. They had 21 which they considered adequately treated that had no results from the medication. Many of these had pelvic disease which contributed to the dysmenorrhea. Six were thought to have rather severe anxiety neurosis.

#### ANALYSIS OF FAILURES

I have attempted to evaluate our 5 cases of fair or poor results. It seems to me that there was some mental factor contributing to the dysmenorrhea. They rather considered themselves martyrs, and expected sympathy for their troubles.

<sup>5</sup> Jones, G. S., and Smith, F., Treatment of dysmenorrhea symptom complex, *Am. J. Obst. and Gynec.* 61:628-633, (March) 1954

One was led to believe by her mother that her trouble was the cross she had to bear for being a woman. The first period she was given two tablets at the onset of pain and got little relief. The second period she took three tablets and had only a few cramps. Thereafter she took four tablets but this medication had lost its newness by that time and had no appreciable effect.

Another was a 32 year old school teacher. She was given three tablets at once. There was no lessening of the cramps but she said she had been chilled when her period started and she wanted to try them again. The next period she took four tablets but there was no diminution of the pain. I cannot account for this failure. She was a very intelligent woman, with no apparent conflicts.

The patient whose cramps were made worse was 40 years old and had two children, 13 and 12 years old. She had always had painful periods and was very nervous at all times. Her blood pressure ranged from 150/80 to 160/90. Her uterus was very firm and slightly larger than normal for a multipara. This may have been a fibrous uterus but I attribute failure to her highly nervous state.

#### GRATITUDE

What about the patients who are relieved by the medication? They are extremely grateful. One girl was having her prescription renewed so frequently that I asked her about it. It seems that she was going to the University and could not bear to see her sorority sisters suffer so she was administering Lutrexin to them.

I would like to quote from a letter I received from a 44 year old woman visiting from Minnesota, who had had severe cramps since puberty, despite having a child of 12. She received some relief from androgrens. She says, "I think we have discovered a miracle. I am better than at any time in the past ten years. The darn stuff is funny—I will think on the second or third day that I am completely over my difficulties, and more or less forget it. Then I will suddenly be hit with severe cramps and the accompany nausea, etc. I run like crazy and take two tablets, and within an hour feel like a new woman. The druggist here had never heard of it, but my doctor had him order it, and upon my report is prescribing it for all his patients with such complaints, and I am sure they are as grateful as I."



Even those who are not completely relieved come back for more tablets when they go through a period without them. That, to me, is the best proof that they are obtaining some benefit.

I believe that this medication deserves more exhaustive trials.

[Reprinted from Northwest Medicine, Vol. 54, pp. 1253-1254, November, 1955—Printed in U.S.A.]

[Reprinted from *Annals of The New York Academy of Sciences*, Volume 75, Article 2 Pages 1037-1038, January 9, 1959]

HAROLD H. BRYANT (*Hynson, Westcott & Dunning, Inc., Baltimore, Md.*)

The procedure used for biological assay and standardization of Lutrexin\* is strictly an *in vivo* method. The test is designed to ascertain the amount of uterine-relaxing hormone present and is not a procedure suitable for assay of relaxin per se. While it is true that Lutrexin preparations do contain some relaxin, the Lutrexin assay procedure will not, and does not, serve as a suitable means of assay of the amount present.

Furthermore, the Lutrexin assay method is not a "uterine strip" or excised muscle procedure. The test involves the entire animal, as the uterus is completely intact with full nerve and blood supply. The material being assayed is injected intravenously or administered orally. In the routine assay, the test material is injected intravenously because of the sharp end point obtained following this route of administration. To anyone familiar with the problems of biological standardization, the desirability of a sharp end point is obvious. The accuracy of a bioassay is directly proportional to the sharpness of a pharmacological response being observed. However, the Lutrexin preparation is also administered orally, and the pharmacological response in decreased uterine activity is readily apparent. The dosage is, of course, higher, and the effect is not as quickly apparent, as is true of all pharmacological agents. The dose required for clinical effectiveness has been determined by the physician administering the drug orally. The laboratory assay of the drug simply determines and standardizes the potency to enable the clinician to administer a "known" amount.

\* Hynson, Westcott & Dunning, Inc., Baltimore, Md.

## Annals New York Academy of Sciences



FIGURE 1. Photographs of assay tracings demonstrating the response to intravenous (a) and orally (b) administered Lutrexin. Note the sharp end point following intravenous injection. Also, observe the effective inhibition of uterine activity following oral administration.

## REFERENCE

The uterine strip is of very limited value, especially with the water-soluble hormones of the ovary. The original publication (Krantz *et al.*, 1950) describing the assay procedure noted that 15 of 26 substances studied, using excised uterine strips, brought about a diminution of uterine activity. The uterine strip is then completely nonspecific and not suitable for assay purposes.

The *in vivo* relaxation of the intact uterus by the ovarian extract has proved to be quite specific. Roughly one hundred substances studied during the past ten years using the Lutrexin assay procedure have failed to give similar inhibition of uterine activity (FIGURE 1).

KRANTZ, J. C., JR., H. H. BRYANT & C. J. CARR. 1950. The action of aqueous corpus luteum extract upon uterine activity. *Surg. Gynecol. Obstet.* 90: 372-375.

## United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND  
WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD  
AND DRUGS, RESPONDENTS*On Petition to Review an Order of the Commissioner of Food  
and Drugs*

Argued February 7, 1972. Decided May 24, 1972.

Before BUTZNER, RUSSELL AND FIELD, Circuit Judges.

Edward Brown Williams (Jan Edward Williams and Harter, Calhoun and Williams, Robert H. Patterson, Jr., and McGuire, Woods and Battle, and John Kyle Warley on brief) for Petitioner, and Gregory B. Hovendon, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, and Peter Barton Hutt, Assistant General Counsel, Food, Drugs and Environmental Health Division, Eugene M. Pfeifer, Attorney, United States Department of Health, Education, and Welfare, on brief) for Respondents: Joel E. Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader and Ross on brief) for Amicus Curiae.

RUSSELL, Circuit Judge:

The appellant, a drug manufacturer, seeks review of a final order withdrawing marketing approval (NDA) of the drug Lutrexin by the Commissioner of Food and Drugs, Department of Health, Education and Welfare.<sup>1</sup> The appellant alleges error in such order of withdrawal (1) for failure to sustain its claim of exemption from withdrawal on account of lack of "substantial evidence" of effectiveness of its drug and, if this claim of exemption is overruled, (2) for denial of a hearing, as required under the applicable statute, on its showing of effectiveness. We reverse.

<sup>1</sup> Section 355(h), 21 U.S.C.

The appellant was granted an approved NDA for Lutrexin in 1952. At that time, the Food, Drug and Cosmetic Act of 1938 conditioned such grant on general recognition of safety of the drug approved. In 1962 the Act was amended to authorize withdrawal of an approved NDA for any drug for which the Commissioner "after due notice and opportunity for hearing", found there was "a lack of substantial evidence of effectiveness."<sup>2</sup> The term "substantial evidence" was defined in the Amendments as "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."<sup>3</sup> There was an exemption from these requirements for drugs, which, *inter alia*, were not covered on the day immediately before the enacting date of the Amendments (i.e., October 9, 1962) by an "effective NDA".<sup>4</sup>

In carrying out his new responsibilities under the Amendments, the Commissioner secured the services of the National Academy of Sciences-National Research Council (NAS-NRC) for reviewing the claims of effectiveness on behalf of any drugs NDA'd between 1938 and 1962.<sup>5</sup> To facilitate its assignment, NAS-NRC set up a Drug Efficacy Study Group and all drug manufacturers with approved NDAs obtained between 1938 and 1962 were directed by the Commissioner to submit to this Group evidence "pertinent to the evaluation of the effectiveness of the(ir) drugs".<sup>6</sup> The appellant submitted to the Group clinical data, investigations and studies in support of the ef-

<sup>2</sup> Section 355(e), 21 U.S.C.

<sup>3</sup> Section 355(d), 21 U.S.C.

<sup>4</sup> "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force \* \* \*, and (C) was not covered by an effective application under section 505 of that Act \* \* \*, the amendments to section 201(p) \* \* \* made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." Section 107(c)(4), appended to Section 321, 21 U.S.C. 1972 Supplement, p. 192.

<sup>5</sup> F.R. 13014, October 6, 1966.

<sup>6</sup> 21 F.R. 13014.

fectiveness for its drug Lutrexin. After considering such data, NAS-NRC concluded that Lutrexin was "possibly effective" but indicated the supporting documentation was inadequate.

The Commissioner advised the appellant of his concurrence with the conclusions of NAS-NRC and, as required by the statute, extended to it an opportunity for a hearing on the proposed withdrawal of the approved NDA for Lutrexin.<sup>7</sup> At such a hearing, the appellant was advised it might "produce evidence and arguments why approval \* \* \* should not be withdrawn."<sup>8</sup> The appellant in due time requested such hearing. Under the Commissioner's regulations, a hearing was required within 90 days after such request, unless the parties agreed otherwise.<sup>9</sup> However, although no delay was agreed on, hearing within such period was not had. The delay on the part of the Commissioner in setting a hearing was due to litigation over the procedure to be followed by it in implementing its efficacy review and in conducting hearings resulting therefrom.<sup>10</sup> It is unnecessary to review the difficulties encountered in developing valid regulations for such hearings. It is sufficient for the issues here that it was not until May 8, 1970, but that the legal objections to the regulations were finally resolved.

During this interregnum when the regulations of the Agency were under challenge and the Commissioner was delaying a hearing, the appellant, whose request for a hearing had been delayed for more than a year, sought in District Court a declaratory judgment to the effect that, under the exemption clause included in the 1962 Amendments, Lutrexin was not a "new drug" on and before October 10, 1962, and was thereby exempt from the requirement of evidence of effectiveness under the Amendments. Such action was dismissed on the ground that primary jurisdiction to resolve the issue of exemption under the Act rested with the Commissioner. No appeal was taken from this dismissal.

While this declaratory action was pending, the Commissioner issued his new regulations detailing the circumstances, under which an applicant might secure a hearing on a proposal by the Commissioner for withdrawal of an effective NDA. By

<sup>7</sup> 33 F.R. 7701.

<sup>8</sup> 34 F.R. 5574.

<sup>9</sup> 21 C.F.R. 130.14(b).

<sup>10</sup> See *Pharmaceutical Manufacturers Association v. Finch* (D.C.Del. 1970) 307 F. Supp. 858; *Upjohn v. Finch* (6th Cir. 1970) 422 F. 2d 944; and *Pfizer, Inc. v. Richardson* (2d Cir. 1970) 434 F. 2d 536.

these regulations, the Commissioner was authorized to deny a hearing, "when it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data".<sup>11</sup>

After the regulation had been legally promulgated, which was more than a year after the appellant had requested a hearing, the Commissioner directed the appellant's attention to these new regulations and suggested that it amend its request for a hearing to comply. Though it contended it had, by its earlier request, perfected its right to a hearing and was not obligated to amend its request, the appellant did, following the dismissal of its declaratory action, submit a considerable amount of clinical medical studies and investigations in support of the claim of effectiveness for its product by way of compliance with the new regulations. The Commissioner, however, dismissed the appellant's request for a hearing on the basis of such showing, finding (1) that its drug was a "new drug" requiring proof of effectiveness, and (2) that its showing of effectiveness was insufficient to demonstrate a "genuine and material issue of fact" under the test of "substantial evidence" as defined in the Amendments. On the basis of these findings it withdrew the approved NDA for Lutrexin. It is from this order that appeal has been taken.

## I

The appellant's claim to an exemption for its drug is easily disposed of. We have held in a related case that a drug covered by a pre-1962 approved NDA, which had not been withdrawn under the procedure set forth in Section 505(e), is not entitled to the exemption granted under Section 107(c)(4) of the Amendments.<sup>12</sup> The appellant's NDA was outstanding and had not been legally withdrawn on October 10, 1962. It cannot ac-

<sup>11</sup> 21 C.F.R. 130.14(b).

<sup>12</sup> *USV Pharmaceutical Corp. v. Richardson*, (4th Cir. 1972) ———  
F. 2d ———.

cordingly claim the benefit of the exemption statute for its drug. While the appellant was entitled to have this issue resolved by the District Court, it was not prejudiced by, and cannot complain of, the refusal by the District Court to exercise jurisdiction. Nor, for that matter, did the appellant appeal and is accordingly without standing in this proceeding to challenge that dismissal.

## II

The crucial issue in this case, however, is posed by the appellant's second contention and revolves about the requirement in the Act that, before the entry of a final order of withdrawal, the applicant be given an "opportunity for hearing". At such a hearing, the procedure adopted by the Commissioner allows the applicant to "produce evidence and arguments to show why approvals of (its drugs) \* \* \* should not be withdrawn."<sup>12a</sup> Of course, the Commissioner might, as he did by his regulations issued in 1970, provide for the denial of a hearing where it clearly appeared from the applicant's own showing there was no "genuine and substantial issue of fact" on which the claim of the applicant might be sustained, *Ciba-Geigy Corp. v. Richardson* (2d Cir. 1971) 446 F. 2d 466, 468. It may be assumed that such regulation, when issued will apply to all pending applications. *U.S. v. Storer Broadcasting Co.* (1956) 351 U.S. 192, 205. But, in applying this regulation and in making his determination thereunder, the Commissioner's discretion is not absolute. Neither due process nor the Administrative Practice Act permits an arbitrary denial in any case where it can be fairly said there are "genuine and substantial issues of fact" in dispute.<sup>13</sup>

Such a denial would, in addition, be violative of the Congressional purpose expressed in the provision for a hearing. And the courts must see that such Congressional purpose is not thwarted by administrative usurpation; or, as the Court said in *Environ-*

<sup>12a</sup> Whether this is too narrow and improperly confines the scope of the hearing, so far as it is adjudicatory, see Davis, *The Requirement of a Trial-Type Hearing*, 70 Har. L. Rev. 193 (1956).

<sup>13</sup> See *Ciba-Geigy Corp. v. Richardson*, *supra*, at p. 468. The question is analogous to that presented by a demand for a hearing in connection with an N.L.R.B. election where the right to a hearing subject to the same general limitations as stated in the Commissioner's regulations, and it would seem the same test of the right to a hearing is applicable. For the rule in such N.L.R.B. case, see *N.L.R.B. v. Bata Shoe Co.* (4th Cir. 1967) 377 F. 2d 821, 825-6; *United States Rubber Co. v. N.L.R.B.* (5th Cir 1967) 373 2d 602, 606; *N.L.R.B. v. Smith Industries, Inc.* (5th Cir. 1968) 403 F. 2d 889, 892-5.



*mental Defense Fund, Inc. v. Ruckelshaus* (D.C.C.A. 1971) 430 F. 2d 584, 596, the courts have "an obligation to ensure that the administrative standards conform to the legislative purpose \* \* \*." Accordingly, only if it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide "substantial evidence" of effectiveness was it proper for the Commissioner to deny the appellant a hearing *before* entering a final order of withdrawal. The judicial test is somewhat the converse of that to be applied in a review of a decision of the Commissioner entered *after* a hearing. In that instance, his decision is to be upheld, if sustained by any substantial evidence.<sup>14</sup> But in determining whether the Commissioner acted within the limits of his discretion on the procedural question of whether a hearing is to be allowed, the test is whether there is any "genuine and substantial" evidence that supports the position of the applicant.

Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that was his burden, a hearing would never be necessary or appropriate. If he, by his showing, convinced or satisfied the Commissioner, the proposed withdrawal would naturally be denied; on the other hand, if he failed to satisfy, then the Commissioner would deny a hearing and order withdrawal. In either event, a hearing would be useless and the Congressional promise of a hearing would be purely illusory. No such exacting standard of proof is required as a basis simply for the right to be heard; as has been observed, all that is required for securing a right to a hearing is that the showing be such that, if accepted, a finding of "substantial evidence" of effectiveness would be supportable. And "substantial" in this connection does not mean "preponderant evidence" or "conclusive evidence". Congress specifically discarded those terms for the milder term "substantial," which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion.<sup>15</sup>

<sup>14</sup> Section 355(h), 21 U.S.C.

<sup>15</sup> In the course of committee deliberation a distinction evolved \* \* \* between two tests the "preponderant evidence" test and the "substantial evidence" test as now specifically defined. Under the former a claim would not be accepted under the new drug section unless it represented the pre-



Applying the foregoing principles, we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. It must be noted that no qualified expert has given an opinion that Lutrexin is ineffective for the uses intended. The NAS-NRC review concluded it was "possibly effective". Neither is there any contention that it is unsafe when used for the purposes intended. The real basis for the determination by the Commissioner that the appellant had failed to make a showing of any genuine issue of fact on the effectiveness of its drug was the conclusion that the various scientific articles and tests submitted by the appellant were not "adequate and well-controlled clinical investigations" within the statutory definition of "substantial evidence". In his decision, the Commissioner sought to point out the deficiencies in the investigations submitted by the appellant which justified this conclusion. In so doing, he did not impugn the competency or qualifications of the scientists and medical experts whose investigations were cited by the appellant in support of its claim. Their professional qualifications, as they appear in the record, are impressive. Their investigations and opinions, some of which have been published in recognized professional medical journals, are, however, dismissed by the Commissioner with the statement that, "No adequate and well-controlled clinical investigations published in the medical literature had been identified."

ponderant view of experts \* \* \* the committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below [that is adequate and well controlled investigations by qualified experts upon the basis of which conclusions made be fairly and responsibly drawn.].

[Application of the substantial evidence test means that] a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which its application is made; or (d) that the conclusions to be drawn by such experts could not fairly and responsibly be derived from their investigation.

8. Rep. No. 1744, 87th Cong., 2nd Sess. Part II, pp. 5-6, and see, 2 U.S. Code Congress. & Administrative News, 87th Cong., 2d Sess., p. 2892 (1962).

In making that statement, he disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director that the clinical tests and investigations submitted by the appellant represented " 'well-controlled' clinical studies". He proceeds to fault two investigations published in an authoritative medical journal, submitted by the appellant, because, "There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced", and "There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance". Another unpublished investigation is dismissed because, "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided". Two published studies by a clinical professor of Obstetrics at the University of Illinois are criticized, in one instance, because "The report does not state the method of patient selection" and "Concomitant medication is not excluded" and, in the other, because "The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor."

Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte*, without a hearing, that it "clearly appears" that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into.

The order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order.

*Reversed.*

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,  
PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION,  
AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF  
FOOD AND DRUGS, RESPONDENTS

*On Petition to Review on Order of the Commissoiner of  
Food and Drugs*

THIS CAUSE came on to be heard upon the petition of Hynson, Westcott and Dunning, Incorporated, for review of an order issued against it by Elliot Richardson, Secretary of Health, Education, Welfare, and Charles C. Edwards, Commissioner of Food and Drugs, on May 31, 1971, in proceedings before the said Agency; and upon a certified list in lieu of a transcript of the record; and the said cause was argued by counsel.

ON CONSIDERATION WHEREOF, it is ordered, adjudged and decreed by the United States Court of Appeals for the Fourth Circuit, that the order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order. The order is reversed.

A True Copy, Teste:  
Filed May 24, 1972.

SAMUEL W. PHILLIPS,  
Clerk.

By J. U. LAYARD,  
Deputy Clerk.

In the Supreme Court of the United States

No. 72-394

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND  
WELFARE, ET AL., PETITIONERS,

v.

HYNISON, WESTCOTT AND DUNNING, INCORPORATED

ORDER ALLOWING CERTIORARI. Filed January 8, 1973

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72-414, 72-528, 72-555, and 72-666, and a total of three hours is allotted for oral argument.

In the Supreme Court of the United States

No. 72-414

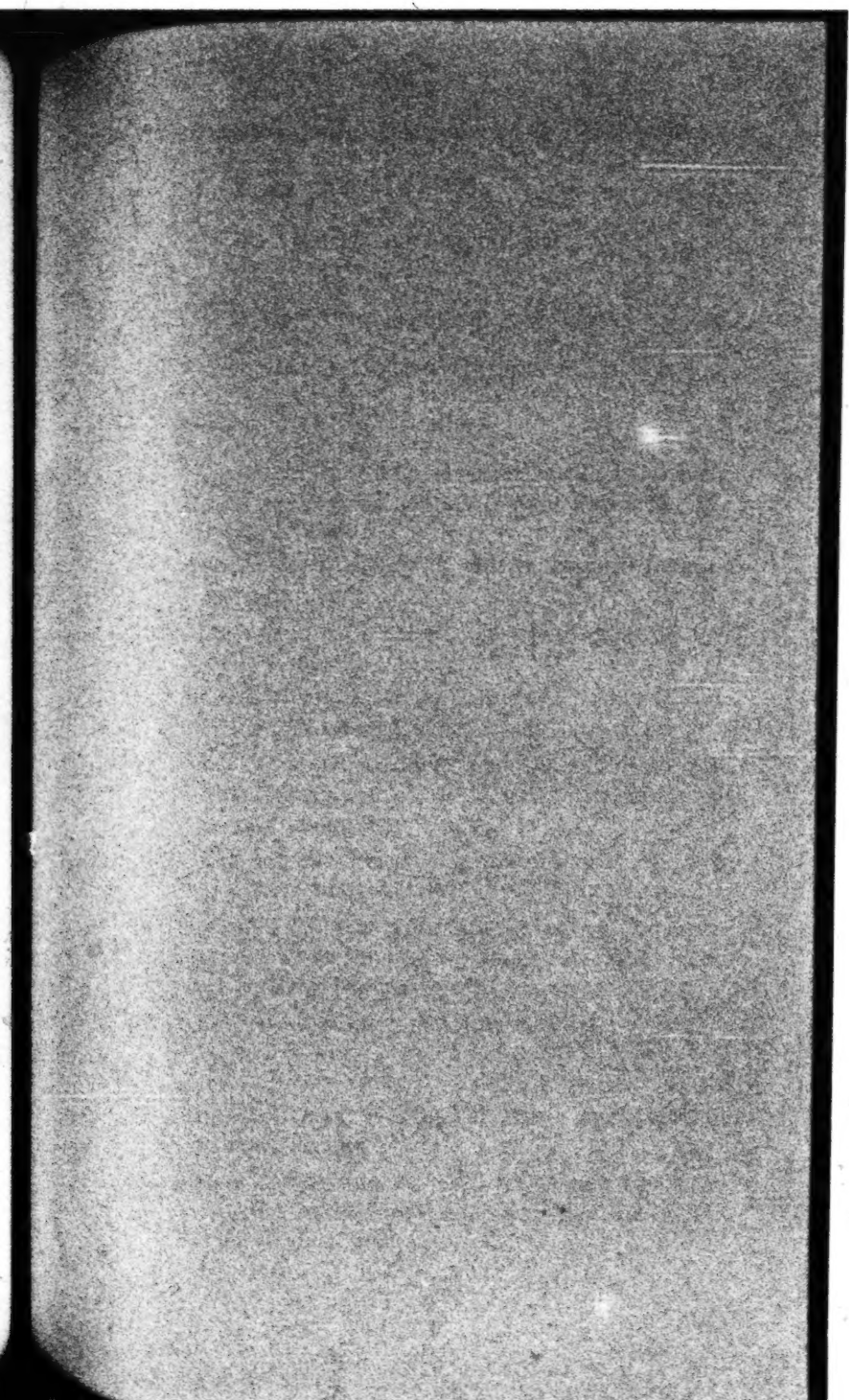
HYNISON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER,

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND  
WELFARE, ET AL.

ORDER ALLOWING CERTIORARI. Filed January 8, 1973

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72-394, 72-528, 72-555, and 72-666, and a total of three hours is allotted for oral argument.



## In the United States Court of Appeals for the Third Circuit

(No. 71-1512)

CIBA CORPORATION, APPELLANT

v.

ELLIOT L. RICHARDSON, ET AL., APPELLEES

## RELEVANT DOCKET ENTRIES

*Date*

1971

- June 15 Copy of Notice of Appeal rec'd. May 21, 1971, filed.  
Record rec'd. June 8, 1971 (except Paper No. 5),  
filed.  
Appearance of Clyde A. Szuch, Esquire for ap-  
pellant, filed.
- July 19 Appearance of Howard S. Epstein, Esquire for ap-  
pellees, filed.
- July 26 Brief and appendix for appellant, received and  
filed. (25 copies).
- Aug. 27 Brief for appellee, filed. (and appendix rec'd for  
the information of the Court.) Certificate of  
service attached.
- Sept. 9 Certificate of service of appellant's brief and ap-  
pendix by mail on July 26, 1971, filed. (2 copies).
- Sept. 14 Consent motion by appellant for leave to file reply  
brief out of time to September 30, 1971, filed.  
(4 copies). Certificate of service attached.
- Sept. 17 Above consent motion granted. *Clerk.*

1972

- Apr. 11 Argued. Coram: Hastie, Van Dusen and Aldisert,  
Circuit Judges.
- May 30 Letter dated May 26, 1972 rec'd from Clyde A.  
Szuch, Esquire for the information of the Court.

*Date*  
1972

- June 5 Opinion Per Curiam (*Hastie, Van Dusen and Aldisert, Circuit Judges*), filed.
- June 5 Judgment affirming the judgment of the District Court filed March 10, 1971, with costs taxed against appellant, filed.
- June 16 Letter, dated June 14, 1972, from Cheryl S. Karner, Esquire, counsel for appellee advising that the Department of Justice intends to waive the costs in this case, filed.
- June 27 Certified judgment in lieu of formal mandate issued.
- June 27 Record returned to Clk of D.C.
- June 29 Receipt for record, filed.
- Oct. 6 Notice of filing of petition for writ of certiorari on Oct. 2, 1972 rec'd from Clerk of S.C. (S.C. No. 72-528), filed.

1973

- Jan. 16 Certified copy of order dated Jan. 8, 1973 rec'd from Clerk of Supreme Court and advising this case is consolidated with Nos. 72-394, 72-414, 72-555 and 72-666, and granting petition for writ of certiorari, filed. (S.C. No. 72-528)
- Feb. 6 Certified copy of appendix and proceedings in this Court forwarded to the Clerk of the Supreme Court pursuant to their request (see letter dated January 29, 1973).

In the United States District Court, District of New Jersey  
Civil Action No. 1210-70

CIBA CORPORATION, A CORPORATION OF THE STATE OF DELAWARE,  
PLAINTIFF,

VS.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND  
WELFARE AND DR. CHARLES C. EDWARDS, COMMISSIONER OF  
FOOD AND DRUGS, DEFENDANTS

COMPLAINT

Ciba Corporation, a corporation of the State of Delaware, having its principal place of business at 556 Morris Avenue, Summit, New Jersey, by way of Complaint, says

FIRST COUNT

1. This action arises under the Federal Food, Drug and Cosmetic Act of 1938 as amended, 21 U.S.C. § 301 et seq. (hereinafter the "Act"), the Drug Amendments Act of 1962, 76 Stat. 780 (1962) and § 9 of the Administrative Procedure Act, 5 U.S.C.A., § 558, and involves an amount in controversy in excess of \$10,000. There exists between the parties an actual controversy, justiciable in nature, as to which plaintiff requires a declaration of its rights by this Court. This Court has jurisdiction of this cause pursuant to the provisions of Title 28 U.S.C.A. §§ 1331, 1337 and 2201-02 and Title 5 U.S.C.A. §§ 701-706.

2. Ciba Corporation is engaged in the manufacture and distribution in interstate commerce of "drugs" as that term is defined in the Act, including a drug marketed under the brand name "Ritonic".

3. Defendant Elliott L. Richardson is the Secretary of the Department of Health, Education and Welfare and charged with the administration of the Act.

4. Defendant Dr. Charles C. Edwards is the Commissioner of Food and Drugs (hereinafter the "Commissioner") and the head of the Food and Drug Administration (hereinafter the "FDA"), a division of the Department of Health, Education and Welfare. He has been delegated by defendant Elliott L. Richardson the authority to administer the Act.



5. Ritonic was developed by Ciba for use, under the supervision of a practitioner licensed by law, primarily for persons who are losing their drive, alertness, vitality and zest for living because of the natural degenerative processes of advancing years. It also benefits patients debilitated or depressed by chronic illness, overwork or recent major surgery.

Ritonic is composed of three types of ingredients. It contains methylphenidate hydrochloride, a central nervous system stimulant which increases alertness and vitality and improves mood and attitude. It also contains male and female hormones which assist the body's capacity to maintain and synthesize protein and otherwise adjust to the decrease in the production of these hormones which occurs with advancing years. The third group of constituents provides a nutritional supplement involving the B-complex of vitamins and the mineral calcium.

6. Ritonic has been marketed commercially since 1959. Its sales volume has averaged approximately 12,000,000 units per year for a total of 134,286,000 units and the yearly gross value of its sales has, in recent years, exceeded \$600,000 with a total of \$6,456,234 in sales since introduction. With the exception of some limited detailing, ceasing in the second quarter of 1966, these sales have not been assisted by any advertising or other promotional devices since 1961.

7. In July of 1958 Ciba submitted to the FDA a New Drug Application (hereinafter "NDA") for Ritonic. The NDA became effective on January 12, 1959.

8. The NDA was submitted in accordance with § 505 (a) of the Act, 21 U.S.C.A. § 355(a), which at that time and since then has provided that all "new drugs", to be marketed legally, must first have an NDA approved by the FDA.

9. At the time the NDA for Ritonic was submitted, the Act defined a "new drug", 21 U.S.C.A. § 321(p), as any drug not generally recognized as being safe. More particularly the Act provided as follows:

(p) The term 'new drug' means—

(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, ... or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

10. At the time the NDA for Ritonic was submitted and became effective the Act provided, 21 U.S.C.A. § 355(d), that the Commissioner should deny approval if among other things he found that the application did not include "(1) . . . adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; [or] . . . (3) upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions. . . ."

11. The NDA for Ritonic contained the results of several clinical investigations involving a total of more than 300 patients and indicating that Ritonic was safe and effective for use under the conditions set forth in its labeling. The NDA also cited several articles published in medical journals, based upon clinical studies and attesting to the safety and effectiveness of Ritonic.

Subsequent to the NDA becoming effective Ciba filed reports supplementing the information in the NDA and bringing to the attention of the FDA the results of additional clinical investigations conducted with respect to Ritonic, the reports of adverse reactions to Ritonic which Ciba had received from the field, and the conclusions of additional published articles. At present Ciba is aware of six articles published in medical and scholarly journals which deal specifically with Ritonic and evaluate it on the basis of clinical trials. Each of these articles has concluded that Ritonic is safe and effective.

12. In 1962 the Act was amended, 76 Stat. 780 (hereinafter the "1962 Amendments"), so as to, *inter alia*, allow the Commissioner to withdraw his approval of a New Drug Application effective prior to the amendment if the manufacturer does not demonstrate to the Commissioner not only that the drug is

safe but that there exists "substantial evidence" that the drug will have the effect it purports or is represented to have under the conditions of use recommended in the labeling thereof. 21 U.S.C.A. § 355(e). The Act specifically provides, 21 U.S.C.A. § 355(e), that prior to withdrawal of approval the manufacturer must be accorded an opportunity for a hearing.

13. The term "substantial evidence" is defined in 21 U.S.C.A. § 355(d) to mean

adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could clearly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

14. In July of 1966 the Commissioner contracted with the National Academy of Sciences—National Research Council (hereinafter the "NAS-NRC") for the review by NAS-NRC panels of drugs given NDA approval prior to 1962 to determine whether there exists substantial evidence of the effectiveness of the such drugs for their suggested uses.

15. On September 12, 1969, the Commissioner caused to be published in the Federal Register (Vol. 34, No. 175) a notice (a copy of which is attached hereto as Exhibit A) stating that, based upon the reports received from the NAS-NRC Drug Efficacy Study Group on Ritonic, he had concluded that there was a lack of substantial evidence that Ritonic was effective for the uses recommended or suggested in its labeling and indicating that he intended to initiate proceedings to withdraw approval of the Ritonic NDA. The notice invited Ciba to submit, within 30 days, pertinent data bearing on the proposal to initiate withdrawal proceedings and further stated that the only data which would be considered acceptable would be adequate and well-controlled studies bearing on the efficacy of Ritonic and not previously submitted.

16. Ciba responded to the Commissioner's notice by letter (a copy of which is attached hereto as Exhibit B) dated October 10, 1969, stating its belief that the evidence of the effectiveness of Ritonic previously submitted to the FDA in the NDA

and the annual reports submitted subsequent thereto, including the clinical investigations and published scholarly articles, constituted substantial evidence of the effectiveness of Ritonic. Ciba also reserved the right to assert that Ritonic is not a new drug and therefore not subject to § 505(a) of the Act, 21 U.S.C.A. § 335(a), which requires new drugs to have an approved NDA.

17. On August 5, 1970, the Commissioner caused to be published in the Federal Register (Vol. 35, No. 151) a notice (a copy of which is attached hereto as Exhibit C) stating that he intended to withdraw his approval of the NDA for Ritonic on the ground that there was a lack of substantial evidence that the drug has the effect which it is purported or represented to have under the conditions of use prescribed or recommended in its labeling. The notice further stated that Ciba could request a hearing for the purpose of presenting evidence as to why the NDA approval for Ritonic should not be withdrawn, that such request for a hearing must be accompanied by a full-factual analysis of the clinical and other investigational data Ciba is prepared to prove in support of the effectiveness of Ritonic, and that the hearing would be denied if in the opinion of the Commissioner the request does not present evidence sufficient to create a substantial issue of fact. The notice additionally provided that if the request for a hearing was denied an order would be issued by the Commissioner withdrawing the approval of the NDA for Ritonic and that upon the effectiveness of this order Ritonic would be considered a new drug, the continued marketing of which would render it subject to regulatory proceedings.

18. On August 31, 1970 Ciba replied to the notice of August 5 availing itself of its right to a hearing although reserving its right to maintain that Ritonic is not a new drug in judicial proceedings. (A copy of Ciba's reply is attached as Exhibit D.)

19. Immediately prior to October 1962, Ritonic was "generally recognized . . . as safe" for its labeled uses and had been used to a material extent and for a material time for such uses. Accordingly Ritonic was no longer a "new drug" under the then existing statutory definition set forth in Paragraph 9 hereof.

20. Because Ritonic was not a "new drug" prior to October 10, 1962, it was not covered by an effective NDA. Consequently, any person could have, immediately prior to October 10, 1962, legally commenced or continued the commercial distribution

of Ritonic for its labeled uses, also without having an NDA in effect.

21. The 1962 Amendment to the Act expanded the definition of a "new drug" so as to require that it be generally recognized not only as safe but also as effective. 76 Stat. 780 § 102(a); 21 U.S.C. 321(p). At the time of that amendment, Congress provided that the amendments should not apply to any drug which on the day immediately preceding the enactment of the amendments, October 9, 1962, was (a) commercially used or sold in the United States, (b) was not a new drug as defined by the Act prior to its amendments, and (c) was not covered by an effective NDA. 76 Stat. 780 § 107(c)(4).

22. As a result of the aforesaid exemption any person could lawfully distribute commercially, after October 10, 1962, any drug which that person had commercially distributed prior to that date and which, on that date, was generally recognized as "safe", even though no NDA was in effect for that drug. Ritonic falls within the exemption in view of the fact that on October 9, 1962, it was being commercially sold in the United States, was not a new drug because generally recognized as "safe" and because it was not covered by an effective NDA.

23. Under the notice of opportunity for hearing, the question for consideration at the hearing offered to plaintiff will not be whether or not Ritonic is a new or an old drug because the FDA lacks the power to adjudicate that issue. The hearing will instead be concerned with whether "there is a lack of substantial evidence" of the effectiveness of Ritonic under the conditions of use stated in its labeling. Plaintiff will consequently be unable to present evidence upon the issue that Ritonic is exempt from the Amendments of 1962 by reason of the aforesaid exemption. Accordingly, plaintiff has exhausted all administrative avenues by which it may seek a determination of its rights on this issue.

24. The introduction into interstate commerce of any "new drug" without an effective NDA is prohibited by 21 U.S.C. 331(d) and 505(a) and a violator is subjected to criminal prosecution, 21 U.S.C. 333, injunctive actions, 21 U.S.C. 331 and proceedings leading to the seizure of the defendants' products. 21 U.S.C. 334. Plaintiff would be subject to such proceedings, at the instance of the defendants, if the NDA for Ritonic were withdrawn and, as stated in Paragraph 17 hereof, defendants have threatened such action. In the event of a successful crimi-

nal prosecution the plaintiff could be fined \$1,000 and its responsible officers could be subject to such fine or a jail term of one year, or both.

25. Plaintiff's business is dependent upon the confidence of the physicians who prescribe its products and the public which uses them. The institution by the defendants of a criminal, injunctive or seizure action would in and of itself substantially and irreparably affect plaintiff's business because of the reliance by many physicians and the public upon the correctness of such an action by a government agency charged with the regulation of drugs.

26. If Ritonic were withdrawn from the market for even a short period of time Ciba would suffer substantial, immediate and irreparable harm. This harm would arise, *inter alia*, from the fact that the withdrawal of Ritonic from the market would cast a cloud over its reputation which its subsequent re-entry into the market could never suffice to completely remove.

27. The safety of Ritonic is well established and has never been questioned. There will be no threat to the public health if Ritonic continues to be marketed pending the outcome of this action.

28. Plaintiff has no adequate remedy at law.

Wherefore, plaintiff demands judgment as follows:

1. Entering a judgment declaring that Ritonic is exempt from the definition of a new drug by the grandfather exemption contained in Section 107(c)(4) of the 1962 Amendments to the Act.

2. Permanently enjoining and restraining defendants, and, pending the final determination of this cause, temporarily enjoining and restraining them from attempting to enforce or enforcing against plaintiff the requirements of the Act relating to "new drugs".

3. Such other and further relief as may be appropriate.

#### SECOND COUNT

1. Plaintiff repeats and makes a part hereof the allegations contained in Paragraphs 1 through 18 of the First Count.

2. As amended in 1962 a new drug is presently defined by the Act, § 201(p), 21 U.S.C.A. § 321(p), as a drug which is not "generally recognized, among experts qualified by scientific training

and experience to evaluate the safety and effectiveness of drugs, as safe and effective under the conditions prescribed, recommended or suggested in the labeling thereof, . . . or . . . any drug [which] . . . has become so recognized but which has not . . . been used to a material extent or for a material time under such conditions."

3. Ritonic is generally recognized among experts qualified by scientific training and experience as safe and effective for use under the conditions recommended in its labeling and has been used to a material extent and for a material time under such conditions.

4. Under the notice of opportunity for hearing, the question for consideration at the hearing offered to plaintiff will not be whether or not Ritonic is a new or an old drug because the FDA lacks the power to adjudicate that issue. The hearing will instead be concerned with whether "there is a lack of substantial evidence" of the effectiveness of Ritonic under the conditions of use stated in its labeling. Plaintiff will consequently be unable to present evidence upon the issue of whether Ritonic is generally recognized as safe and effective. Accordingly, plaintiff has exhausted all administrative avenues by which it may seek a determination of its rights on this issue.

5. Plaintiff repeats and makes a part hereof the allegations contained in paragraphs 24 through 28 of the First Count.

WHEREFORE, plaintiff demands judgment as follows:

1. Entering a judgment declaring that Ritonic is not a new drug within the definition of Section 201(p) of the Act as amended, 21 U.S.C. § 321(p), because it is generally recognized as safe and effective.

2. Permanently enjoining and restraining defendants, and, pending the final determination of this cause, temporarily enjoining and restraining them from attempting to enforce or enforcing against plaintiff the requirements of the Act relating to "new drugs."

3. Such other and further relief as may be appropriate.

PITNEY, HARDIN & KIPP,  
*Attorneys for Plaintiff, Ciba Corporation.*

By CLYDE A. SZUCH,

*A Member of the Firm.*

Dated: September 4, 1970.



31 F.R. 9426 (July 9, 1966)

*Food and Drug Administration*

**NEW DRUGS**

**Reports of Information for Drug Effectiveness**

The National Academy of Sciences-National Research Council (NAS-NRC) has agreed to assist the Food and Drug Administration in its review of the claims of effectiveness for drugs cleared through the new-drug procedures from 1938 until October 10, 1962. To facilitate this review and a determination of whether there may be ground for invoking section 505(e) of the Federal Food, Drug, and Cosmetic Act, and to provide each holder of such an approved new-drug application an opportunity to present for the consideration of the reviewing experts the best data available to support the medical claims, this order is entered pursuant to section 505 of the act:

1. Each holder of a new-drug application approved between 1938 and October 10, 1962, shall report the following, in duplicate, preferably on forms which have been devised by the National Academy of Sciences-National Research Council and which are available for the purpose from the Food and Drug Administration or any of its offices:

- a. New-drug application number, date originally approved, and whether Rx or OTC drug.
- b. Brand name of drug or preparation.
- c. Applicant's (firm's) name and address.
- d. Quantitative formula using established (non-proprietary) name of active ingredients.
- e. Dosage form and route of administration. Where a new-drug application covers different routes of administration, separate forms should be used.
- f. Current labels and package inserts (attach 10 copies of each to original of form; 1 copy of each to duplicate).
- g. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package



insert, or brochure. Approximately 5 to 10 key references, if available (attach 10 copies of the list to original of form and 1 copy to duplicate).

h. Unpublished articles or other data pertinent to an evaluation of the claims (one copy only; attach to duplicate).

2. This report shall be made as promptly as possible and no later than 60 days from the date of this publication in the **FEDERAL REGISTER**, shall be plainly marked on the outside of the envelope or package "Special Drug Report," and shall be addressed to the Director, Bureau of Medicine (or Director, Bureau of Veterinary Medicine, in the case of veterinary drugs), Food and Drug Administration, Washington, D.C. 20204.

3. The submission of this special report may be made without prejudice to any person's contention that he is not required by law to make the report.

4. This order is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(j), 52 Stat. 1052, as amended, 76 Stat. 732, 21 U.S.C. 355(j)) and under the authority delegated to the Commissioner of Food and Drugs by the Secretary of Health, Education, and Welfare (21 CFR 2.120; 31 F.R. 3003).

Dated: July 6, 1966.

JAMES L. GODDARD,  
*Commissioner of Food and Drugs.*

[F.R. Doc. 66-7489; Filed, July 8, 1966; 8:47 a.m.]

SEPTEMBER 5, 1969.

NDA 11-591 Ritonic ACC 1320

Certified Mail Return Receipt Requested

CIRA PHARMACEUTICAL COMPANY,  
556 Morris Avenue,  
Summit, New Jersey 07901

GENTLEMEN: Enclosed is the report we have received from the National Academy of Sciences-National Research Council Drug Efficacy Study concerning their evaluation of the claims for your drug product identified above.

An announcement will soon be published in the Federal Register concerning this drug product.

Sincerely yours,

PAUL A. BRYAN, M.D.,  
Special Assistant for Drug Efficacy  
Study Implementation,  
Bureau of Medicine.

Enclosure.

National Academy of Sciences—National Research  
Council—Division of Medical Sciences

# DRUG EFFICACY STUDY

## FORM A

(To be submitted in duplicate by applicant)

1. NDA Number: 11-591 E-01.
2. Date Originally Approved: 9/3/58.
3. Rx X OTC—.
4. Brand Name: Ritonic.
5. Applicant's Name and Address: CIBA Pharmaceutical Company, 555 Morris Avenue, Summit, New Jersey 07901.
6. Quantitative Formula:

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label):

	Amount (per tablet, per ml., etc.)
Methylphenidate hydrochloride.....	5 mg./capsule
Methyltestosterone .....	1.25 mg./capsule
Ethinyl estradiol.....	5 meg./capsule
Thiamin .....	5 mg./capsule
Riboflavin .....	1 mg./capsule
Pyridoxine hydrochloride.....	2 mg./capsule
Vitamin B <sub>12</sub> activity.....	2 meg./capsule
Ricofinamide .....	25 mg./capsule
Dicalcium phosphate.....	250 mg./capsule

7. Dosage form (tablets, etc.): Capsules.
8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.): Oral.
9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)
11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.
12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

### PANEL ON PSYCHIATRIC DRUGS

#### INDICATIONS

- I. Ritonic is for patients who are losing their drive, alertness, vitality, and zest for living because of the natural degenerative changes of advancing years*

**EVALUATION:** Ineffective.

**COMMENTS:** All references supporting the utility of Ritonic itself (as distinct from the Ritalin it contains) are uncontrolled and testimonial although generally positive while focused on aged patient populations. No clear indications for combining these heterogenous ingredients in a single capsule exists.

The Panel considers the combination to be ineffective for this indication, and points out the absence of controlled studies of the individual ingredients vs. the combination, of the individual ingredients vs. each other, and of the combination itself.

#### DOCUMENTATION:

1. Bachrach, S. A new stimulant supplement for the geriatric patient. *J. Amer. Geriatr. Soc.* 7:408-409, 1959.
2. Bare, W. W. A stimulant for the aged; observations on a methylphenidate-vitamin-hormone combination (ritonic). *J. Amer. Geriatr. Soc.* 8:292-297, 1960.
3. Bare, W. W., and D. Y. P. Lin. A stimulant for the aged; II. Long-term observations with a methylphenidate-vitamin-hormone combination (ritonic). *J. Amer. Geriatr. Soc.* 10:539-544, 1962.

4. George, R. B., and C. H. Lee. A stimulant supplement for the chronically ill: three-month study in a tuberculosis ward. *J. Louisiana Med. Soc.* 117:239-241, 1965.

5. Natenshon, A. L. Ritonic—a new geriatric supplement. *Journal of the American Geriatrics Society* 6: 534-538, 1958.

*II. Ritonic also benefits patients debilitated or depressed by chronic illness and overwork*

EVALUATION: Ineffective.

COMMENTS: Same as for Indication I.

DOCUMENTATION: Same as for Indication I.

*III. Ritonic is indicated for patients who are recuperating from illness or surgery*

EVALUATION: Ineffective.

COMMENTS: Same as for Indication I.

DOCUMENTATION: Same as for Indication I.

Approved by

\_\_\_\_\_,  
Chairman.

## RITONIC ®

### Stimulant and Vitamin-Hormone Supplement

#### DESCRIPTION

Ritonic is a preparation designed to improve mood and maintain vitality. Each Ritonic capsule contains Ritalin-hydrochloride (methylphenidate hydrochloride (CIBA)—a mild stimulant—and a balanced complement of vitamins, calcium, and hormones. With Ritonic, patients benefit from the mental and physical alerting effects of Ritalin hydrochloride (methylphenidate hydrochloride) as well as anabolic stimulation and nutritional support.

Each Ritonic capsule contains 5 mg methylphenidate hydrochloride, 1.25 mg methyltestosterone, 5 micrograms ethinyl estradiol, 5 mg thiamin (vitamin B<sub>1</sub>), 1 mg riboflavin (vitamin B<sub>2</sub>), 2 mg pyridoxine hydrochloride (vitamin B<sub>6</sub>), 2 micrograms vitamin B<sub>12</sub> activity (present as cobalamin concentrate), 25 mg nicotinamide, and 250 mg dicalcium phosphate.

Two Ritonic capsules supply ten times the M.D.R.\* of vitamin B<sub>1</sub>, one and one-half times the M.D.R. of vitamin B<sub>2</sub> and five times the M.D.R. of nicotinamide. The need in human nutrition for vitamin B<sub>6</sub> and B<sub>12</sub> has not been established.

#### INDICATIONS

Ritonic is for patients who are losing their drive, alertness, vitality and zest for living because of the natural degenerative changes of advancing years. Ritonic also benefits patients debilitated or depressed by chronic illness, overwork, etc., as well as those recuperating from illness or surgery.

#### CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to methylphenidate since the drug may aggravate these symptoms.

Methylphenidate is contraindicated in patients with glaucoma and in patients with epilepsy.

Ethinyl estradiol is contraindicated in females in the presence of breast or genital carcinoma.

Methylestosterone is contraindicated in the presence of carcinoma of the prostate and the breast in males or severe liver damage.

#### WARNINGS

Ritonic should not be used in patients with severe mental depression.

Because methylphenidate may mask normal fatigue states induced by overexertion, Ritonic should not be used to increase mental or physical capacities beyond physiological limits.

Do not give MAO inhibitors to patients taking Ritonic.

#### RITONIC

Bare, W.W., *A stimulant for the Aged, Observations on the Methylphenidate-Vitamin-Hormone Combination (Ritonic)*, Journal of the American Geriatrics Society 8 (4): 292-297, April 1960.

Natenshon, A.L., *Ritonic—A New Geriatric Supplement*, Journal of the American Geriatrics Society, 6 (7): 534-538, July 1958.

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\*Minimal daily requirement.

Bachrach, S., *A New Stimulant Supplement for the Geriatric Patient*, Journal of the American Geriatrics Society, 7 (5): 408-409, May 1959.

George, R.B., and Lee, C.H., *A Stimulant Supplement for the Chronically Ill: Three-Month Study in a Tuberculosis Ward*, Journal of the Louisiana Medical Society, 117 (7): 239-241, July 1965.

Bare, W.W., and Lin, D.Y.P., *A Stimulant for the Aged. II. Long-Term Observations with a Methylphenidate-Vitamin-Hormone Combination (Ritonic)* Journal of the American Geriatrics Society, 10 (6): 539-544, June 1963.

Jacobson, A., *The Use of Ritalin in Psychotherapy of Depressions of the Aged*, The Psychiatric Quarterly, p. 1-10, July 1958.

Landman, M.E., Preisig, R., Perlman, M., *A Practical Mood Stimulant*, J. Med. Soc. New Jersey, 55: 1-4, 1958.

Ferguson, J.T., and Funderburk, W.H., *Improving Senile Behavior with Reserpine and Ritalin*, JAMA, 160: 259-263, 1958.

Natenshon, A.L., *Clinical Evaluation of Ritalin*, Dis. of the Nervous Systems, 17: 392-396, 1956.

34 F.R. 14339 (September 12, 1969)

### *Food and Drug Administration*

CETYLPIRIDINIUM CHLORIDE WITH BENZYL ALCOHOL THROAT LOZENGES AND CERTAIN OTHER DRUGS

Drugs for Human Use; Drug Efficacy  
Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Cepacol Throat Lozenges containing cetylpyridinium chloride 1:1500 and 0.3 percent benzyl alcohol; marketed by the Wm. S. Merrell Co., Division of Richardson-Merrell, Inc., 110 Amity Road, Cincinnati, Ohio 45215 (NDA 5-422).

2. Aclor Capsules containing 5 grains glutamic acid hydrochloride per capsule; marketed by Cole Pharmacal

Co., Inc., 3721 Laclede Avenue, St. Louis, Mo. 63108 (NDA 4-484).

3. Flanithin Capsules containing 325 milligrams glutamic acid hydrochloride per capsule; marketed by Table Rock Laboratories, Inc., 812 Hampton Avenue, Greenville, S.C. 29601 (NDA 1-002).

4. Ritonic Capsules containing 5 milligrams methylphenidate hydrochloride, 1.25 milligrams methyltestosterone, 5 micrograms ethinyl estradiol, 5 milligrams thiamine mononitrate, 1 milligram riboflavin, 2 milligrams pyridoxine hydrochloride, 2 micrograms cobalamin concentrate, 25 milligrams niacinamide, and 250 milligrams dibasic calcium phosphate per capsule; marketed by Ciba Pharmaceutical Co., 556 Morris Avenue, Summit, N.J. 07901 (NDA 11-591).

5. Am Plus Improved Capsules containing per capsule 5 milligrams dextroamphetamine sulfate, 5 milligrams hydroxyzine hydrochloride, and Vitamin A palmitate, ergocalciferol, thiamine mononitrate, riboflavin, pyridoxine hydrochloride, niacinamide, sodium ascorbate, ascorbic acid, calcium pantothenate, cobalamin concentrate, dibasic calcium phosphate, cobaltous sulfate, cupric sulfate, potassium iodide, ferrous fumarate, manganous sulfate, sodium molybdate, magnesium sulfate, potassium sulfate and zinc sulfate; marketed by J. B. Roerig & Co., Division, Chas. Pfizer & Co., Inc., 235 East 42d Street, New York, N.Y. 10017 (NDA 11-852).

6. Liquid Germicidal Detergent containing 2½ percent benzethonium chloride; marketed by Parke, Davis and Co., Joseph Campau at the River. Detroit, Mich. 48232 (NDA 5-616).

7. Phemerol Tincture containing benzethonium chloride 1:500, and alcohol 65 percent; marketed by Parke, Davis and Co. (NDA 4-232).

8. Phemerol Solution containing benzethonium chloride 1:750; marketed by Parke, Davis and Co. (NDA 4-231).

9. Phemerol Topical containing 3 percent benzethonium chloride; marketed by Parke, Davis and Co. (NDA 5-113).

10. Bilcain Tablets containing 3 grains ox bile extract, ⅛ grain aloin, and ½ grain cascara sagrada extract per tablet; marketed by Cole Pharmacal Co., (NDA 3-420).

11. Ethylene Disulphonate (Allergosil Brand) Ampoules containing ethylene disulfonate in a dilution of  $10^{-10}$  sterile water for injection; marketed by Spicer-Gerhart Co., 23 North Sycamore, Pasadena, Calif. 91107 (NDA 5-127).

12. Alertonic Elixir containing in each 45 cubic centimeters: 2 milligrams pipradrol hydrochloride, 10 milligrams thiamine hydrochloride, 5 milligrams riboflavin, 1 milligram pyridoxine hydrochloride, 50 milligrams niacinamide, 100 milligrams choline chloride, 100 milligrams inositol, 100 milligrams calcium glycerophosphate, 1 milligram manganous sulfate, 1 milligram magnesium acetate, 1 milligram zinc acetate, 1 milligram ammonium molybdate, and alcohol; marketed by The Wm. S. Merrell Co. (NDA 10-740).

The Food and Drug Administration has concluded that there is a lack of substantial evidence that these drugs are effective for all the uses recommended or suggested in their labeling and that each component of the combination drugs contributes to the total effects claimed for such drugs.

The Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the new drug applications for these drugs. Prior to initiating such action, however, the Commissioner invites the holders of new drug applications for these drugs, and any interested person who may be adversely affected by removal of these drugs from the market, to submit any pertinent data bearing on the proposal within 30 days following the date of publication of this notice in the FEDERAL REGISTER. The only material which will be considered acceptable for review must be well-organized, and consist of adequate and well-controlled studies bearing on the efficacy of the products and not previously submitted.

This announcement of the proposed action and implementation of the NAS-NRC report for the above drugs is made to give notice to persons who might be adversely affected by withdrawal of these drugs from the market. Promulgation of an order withdrawing approval of the new drug applications will cause any such drug on the market offered for these uses, to be a new drug for which an approved new drug application is not in effect, and will make it subject to regulatory action.



A copy of the NAS-NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number, DESI 1002, and should be directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

Request for NAS-NRC report: Press Relations Office (CE-300).

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (MD-16), Bureau of Medicine.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended, 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: September 4, 1969.

HERBERT L. LEY, Jr.,  
*Commissioner of Food and Drugs.*

[F.R. Doc. 69-10875; Filed, Sept. 11, 1969; 8:45 a.m.]

OCTOBER 10, 1969.

NDA 11-591 Ritonic

Re: DESI 1002.

SPECIAL ASSISTANT FOR DRUG EFFICACY  
STUDY IMPLEMENTATION,  
*Bureau of Medicine (MD-16),  
Food and Drug Administration,  
200 C Street, S.W.,  
Washington, D.C. 20204.*

GENTLEMEN: The Federal Register of September 12, 1969, (Vol. 34, No. 175) contained a notice that the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the new application for Ritonic, No. 11-591.

CIBA wishes to advise you that it does not agree with the conclusions set forth in that notice that there is a lack of substantial evidence that Ritonic is effective for the uses recommended or suggested in its labeling and that each component of

the combination contributes to the total effect claimed for the drug.

The September 12, 1969, notice provided for the submission within a thirty-day period of pertinent data "not . . . previously submitted". In addition to the material submitted by CIBA in the "Special Drug Report" for Ritonic filed in response to the Federal Register notice dated July 9, 1966, (Vol. 31, No. 132), we submit herewith, by incorporation by reference, the data and material heretofore submitted and referred to in the Ritonic New Drug Application, in supplements thereto, and in periodic and in all other reports filed by CIBA with the Food and Drug Administration with regard to Ritonic.

CIBA reserves all rights to assert that Ritonic is not a new drug and is not subject to the provisions of Section 505 of the Food, Drug and Cosmetic Act as amended (21 U.S.C. 355).

We wish to advise you that should the Commissioner initiate proceedings to withdraw approval of the new drug application for Ritonic, we reserve our right to avail ourselves of the opportunity for hearing provided for in Section 505 of the Food, Drug and Cosmetic Act (21 U.S.C. 355).

Sincerely yours,

CIBA PHARMACEUTICAL COMPANY,  
JOSEPH S. HARUN, M.D.,  
*Executive Director,*  
*Drug Regulatory Affairs Division.*

35 F.R. 12495 (August 5, 1970)

*Food and Drug Administration*

[Docket No. FDC-D-207; NDA No. 11-591]

CIBA PHARMACEUTICAL Co.

Ritonic Capsules; Notice of Opportunity for Hearing on  
Proposal To Withdraw Approval of New-Drug Application

In an announcement (DESI 1002) published in the FEDERAL REGISTER of September 12, 1969 (34 F.R. 14339), CIBA Pharmaceutical Co., 556 Morris Avenue, Summit, N.J. 07901, the holder of new-drug application No. 11-591 for Ritonic Capsules containing 5 milligrams methylphenidate hydrochloride, 1.25

milligrams methyltestosterone, 5 micrograms ethinyl estradiol, 5 milligrams thiamine mononitrate, 1 milligram riboflavin, 2 milligrams pyndoxine hydrochloride, 2 micrograms cobalamin concentrate, 25 milligrams niacinamide, and 250 milligrams dibasic calcium phosphate per capsule, as well as any other interested person, were invited to submit pertinent data bearing on the intention of the Commissioner of Food and Drugs to initiate proceedings to withdraw approval of the new-drug application.

CIBA responded to the announcement: however, the information submitted does not provide substantial evidence of effectiveness of the drug for its recommended uses, that is: In patients who are losing their drive, alertness, vitality and zest for living because of the natural degenerative changes of advancing years; patients debilitated or depressed by chronic illness or overwork: and patients who are recuperating from illness or surgery.

Therefore, notice is given to CIBA Pharmaceutical Co. and to any other interested person who may be adversely affected that the Commissioner proposes to issue and order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c)) withdrawing approval of new-drug application No. 11-591 and all amendments and supplements thereto for Ritonic Capsules on the grounds that new information before the Commissioner with respect to such drug, evaluated with the evidence available to him when the application was approved, shows there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the applicant, and any interested person who would be adversely affected by an order withdrawing such approval, an opportunity for a hearing to show why approval of the new-drug application should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing the same components and offered for the same conditions of use to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the **FEDERAL REGISTER**, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-62, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing;
- or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the new-drug application. Failure of such persons to file a written appearance of election within said 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing, they must file within 30 days after the publication of this notice in the **FEDERAL REGISTER** a written appearance requesting the hearing, giving the reasons why approval of the new-drug application should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data they are prepared to prove in support of their opposition to this notice. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that no genuine and substantial issue of fact preclude, the withdrawal of approval of the application, the Commissioner will enter an order on these data, making findings and conclusions on such data.

If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after

the expiration of such 30 days unless the hearing examiner and the person(s) requesting the hearing otherwise agree (35 F.R. 7250, May 8, 1970).

This notice is issued pursuant to provisions of the Federal Food, Drug and Cosmetic Act (sec. 505, 52 Stat. 1052-53, as amended; 21 U.S.C. 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: July 24, 1970.

SAM D. FINE,

*Acting Associate Commissioner for Compliance.*

[F.R. Doc. 70-10145, Filed, Aug. 4, 1970; 8:48 a.m.]

AUGUST 31, 1970.

NDA 11-591, Ritonic Capsules

HEARING CLERK,

*Department of Health, Education, and Welfare,  
Room 6-62, 5600 Fishers Lane,  
Rockville, Maryland 20852*

DEAR SIR: CIBA Pharmaceutical Company, a Division of CIBA Corporation, hereby makes a written appearance in response to the Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Drug Application No. 11-591 (Ritonic Capsules) published in the Federal Register of August 5, 1970.

As provided for in Section 505(e) of the Food, Drug and Cosmetic Act (21 U.S.C. 355) CIBA hereby elects to avail itself of the opportunity for a hearing.

The August 5, 1970, Notice of Opportunity for Hearing requires the applicant electing to avail itself of the opportunity to state the reasons why approval of the New Drug Application should not be withdrawn. For the reasons set forth in the complaint filed by the Pharmaceutical Manufacturers Association in the United States District Court for the District of Delaware on July 23, 1970, this is an improper demand.

We wish to advise you that it is CIBA's position that Ritonic Capsules are not now a new drug under the Food, Drug and Cosmetic Act, as amended and that the amendments of 1962 are not applicable to that drug. Therefore, this election to avail ourselves of the opportunity for a Hearing is made with

a reservation of the right to establish these facts in the administrative proceedings, or in judicial proceedings, or both.

Sincerely yours,

JOSEPH S. HARUN, M.D.,  
Executive Director,  
Drug Regulatory Affairs Division.

JSH:lar

35 F.R. 15253 (September 30, 1970)

*Food and Drug Administration*

[Docket No. FDC-D-207; NDA No. 11-591]

**CIBA PHARMACEUTICAL Co.**

**Ritonic Capsules; Notice of Withdrawal of Approval of New-Drug Application**

On August 5, 1970, there was published in the Federal Register, 35 F.R. 12495. A notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug application No. 11-591 for Ritonic Capsules and all amendments and supplements thereto on the ground that there is a lack of substantial evidence that Ritonic Capsules have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

CIBA Pharmaceutical Co., a division of CIBA Corp., Summit, N.J. 07901, holder of NDA No. 11-591 for Ritonic Capsules, filed a letter requesting a hearing pursuant to the August 5, 1970 publication, but did not file any data to support such request and provided no reasons why approval of NDA No. 11-591 should not be withdrawn, as required by the August 5, 1970, publication. The Commissioner of Food and Drugs concludes there are no genuine substantial issues of fact to justify a hearing (35 F.R. 7250; May 8, 1970).

The Commissioner of Food and Drugs, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (Section 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds that on the

basis of new information before him with respect to said drug, evaluated together with the evidence available to him when the application was approved, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing finding, approval of the above new-drug application, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document.

Dated: September 21, 1970.

SAM D. FINE,  
*Associate Commissioner for Compliance.*

[F.R. Doc. 70-12989; Filed, Sept. 29, 1970; 8:46 a.m.]

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EXCERPTS FROM TRANSCRIPT OF PROCEEDINGS IN DISTRICT  
COURT, JANUARY 11, 1971

[23] [Mr. SZUCH.] \* \* \*

All of the correspondence from the Commission to my client, Ciba, has been: "Present evidence on safety and efficacy." The invitation to submit and the invitation to participate in the hearings obviously stem from a conclusion formed by the Commission that they have a new drug. Therefore, under the statute you must establish safety and efficacy.

The COURT. Suppose the Court of Appeals reverses the determination? Reverses the determination of the Commissioner below? You would be all right then. You would get a—

Mr. SZUCH. I have nothing in the record before the Court of Appeals on the issue at all, your Honor.

The COURT. The Court of Appeals is either going to affirm or reverse or remand.

Mr. SZUCH. Based on the record from the Court of Appeals, on this issue it would have to affirm.

Neither side has anything in the record, I don't believe—Counsel for the government and I have not seen the record and I don't believe that Ciba has submitted any information which would constitute part of this record relating to the issue of general recognition of safety and efficacy, and we can ask the government's attorney right now if the government has.

Mr. ANDERSON. Ciba has submitted a nine-item bibliography which referenced part of which was in the medical [24] literature together with a fifty-page 690-item bibliography concerning all of the constituents of the drugs which cite references to the world medical literature concerning the safety and efficacy of Ritonic capsules. This bibliography, together with the available reprints, is in the record.

Mr. SZUCH. That information is submitted on the issue of safety and efficacy, but there is no evidence in the record of general recognition of safety and efficacy which is a fair different issue from the issue which is now before the Court of Appeals or that may be before the Court of Appeals, if this Court decides that it doesn't have jurisdiction.

The COURT. While that case is pending in the Court of Appeals for the Second Circuit, is the government doing anything to Ciba? Is it seizing the drug?

Mr. SZUCH. No, it is not.

The COURT. Does it intend to before that Court decides the issue?

Mr. SZUCH. The government and we have entered into an agreement, your Honor, on an informal basis, that no action will be taken without giving us prior notice to that effect pending the resolution of the matter and we would expect, your Honor, as I indicated, as far as the Second Circuit decision is concerned, or as far as the appeal is concerned, depending on your Honor's ruling. If your Honor rules that you have jurisdiction here which we think you do, [25] we will immediately dismiss the Court of Appeals action because we don't think that you can or should go both ways.

If we are correct in the position that we have advanced before your Honor, our notice of appeal in the Court of Appeals is properly dismissable on motion.

Mr. ANDERSON. If I may, your Honor, I would just like to— and, again, I don't wish to engage in any extended colloquy with counsel on this now—but, for the record, counsel did mention it. The nature of whatever informal agreement may have been made between Mr. Szuch and myself is not quite as he puts it. At the time that the T.R.O. was in question and there was a point in time when Ciba was going to come before you on T.R.O., we did informally work out an agreement whereby at that time no action would be taken with respect to this drug until Ciba had been contacted again and fully apprised of the



agency's position. I think now, your Honor, that has been achieved, and I should point out to your Honor that in this regard that the statute provides—by "the statute" I refer to Section 505(h)—that a stay is available from the Court of Appeals on the application of the—

The COURT. Do you think that the government will voluntarily agree to a stay pending the decision of the Court of Appeals?

Mr. ANDERSON. I am not prepared to answer that question [26] your Honor, until the application is made to the Court of Appeals for such a stay and it was made by the Ciba Corporation. They made no such application.

The COURT. I understand. Mr. Szuch says that he is not interested in my Court—if I take it on.

Mr. ANDERSON. Your Honor, if I may, I have no comment on the on-again off-again approach to the separate service, but I believe that here for our purposes it simply will not wash to say that a statute which grants authority to the Court of Appeals to review a final order on the question which resolves all available evidence on the safety and efficacy of a particular drug and whether or not it is generally recognized by the experts well qualified in their field as safe and effective, somehow withhold authority from the Court of Appeals to determine the fundamental question of whether or not the drug involved is a new drug. That is, whether it is generally recognized as safe and effective. The petitioners—the plaintiff—has cited no case for that proposition. To the contrary, and as your Honor pointed out, the expertise as a matter of primary jurisdiction, is very important and has been judicially recognized and preserved in a variety of cases which we have cited to your Honor. More particularly, although, of course, not binding on your Honor, the propriety of raising the not-a-new-drug issue and the grandfather issue at the agency level for later review by the [27] Court of Appeals has been expressly recognized by Judge Northrup in *Hinson Westcott v. Dunning*, down in Delaware.

The COURT. You will agree with me that under the declaratory judgment that it would be discretionary whether or not I entertain this application?

Mr. ANDERSON. Your Honor, it is in any event within your Honor's discretion to issue the relief sought, and I think regardless of the cases cited, no factual case here has been made out which would authorize or warrant your Honor's assertion of

your discretionary jurisdiction to grant the relief that the plaintiff seeks.

The COURT. Well, you are asking for two things, and we know we are not talking about the merits. We eliminated that. You are talking only about jurisdiction now.

Mr. ANDERSON. That is correct, and we are asking now that the action be dismissed.

The COURT. Mr. Szuch, what about that? It could be if I had jurisdiction. Under the Declaratory Judgment Act I could in the exercise of a sound discretion say to you, "I am sorry, I will not entertain the action here because you have got one pending in the Court of Appeals for the Second Circuit."

Now, it would seem to me, and I have given this a lot of thought, that because of the nature of the application this is new law, really. A lot of these cases just recently [28] coming down, and some of them—You can see that some of them have not been clearly thought out, but that is neither here nor there. I feel that under all of the circumstances that even assuming that I do have jurisdiction to determine the question that you put to me, that in the exercise of my discretion I would decline and refuse to exercise that jurisdiction and grant the government's motion, and leave you to pursue your remedy in the Court of Appeals.

Mr. SZUCH. Your Honor, in order to reach that result I think your Honor would also have to reach the conclusion, contrary to what we have put forward, that we have an adequate remedy in the Court of Appeals. We would submit to your Honor that we do not. The issue that we would expect to move before your Honor of general recognition of safety and effectiveness is one which we do not believe is before the Court of Appeals.

The COURT. Is before the Court of Appeals.

Mr. SZUCH. We have not produced a record of that issue before the Commission. We have no record on that before the Court of Appeals. Indeed, if we would expect that that issue is to be adjudicated, that many experts would have to be gotten, and we would have to take the depositions of some of the experts of the government on whom they intend to rely and there is a great factual investigation and presentation which must be made to some trier of the facts, and I don't really believe that the [29] Court of Appeals is going to sit as a trial Court or should sit as a trial Court on that issue. They are a reviewing Court to review the propriety or impropriety of the Commissioner's action.

The COURT. I agree with that. That is what it is doing, but how would you be hurt if you had this issue, whatever it may be, or as narrow as you want to construe it to be, that is now pending before the Court of Appeals? How would you be hurt if the matter is left there with a stay application that the——

Mr. SZUCH. Let us assume that the Court of Appeals resolves the issue and affirms the Commissioner without getting to the issue that I am trying to try before your Honor which I submit is very possible on the record going to the Court of Appeals. We would then be faced with a seizure.

The COURT. And then this Court would be available.

Mr. SZUCH. That is correct, which then means that we will have to subject the Ciba Corporation to possible criminal action.

The COURT. If they seize you, you come in to see me at any time. Then we have cases which clearly indicate that the District Court has jurisdiction. When there has been a seizure.

Mr. SZUCH. That is correct, your Honor, but may I suggest that if your Honor concludes you have jurisdiction [30] when there is a seizure, why would there be anything different for declaratory judgment relief? There is nothing peculiar or different about an action for a declaratory judgment. We have got to find initial jurisdiction. It is peculiar in a sense that you must exercise your discretion, but other than that whether it be a declaratory judgment or a suit as of right, such as a seizure action, we must first posit the action on the Court having jurisdiction.

The COURT. I have jurisdiction in a seizure case. What do I decide in a seizure case? Whether the seizure was right or wrong.

Mr. SZUCH. And in that connection, your Honor——

The COURT. This is much narrower then.

Mr. SZUCH. No, it won't be, because in order to decide whether the seizure was right or wrong the defense which would be raised possibly, and I don't know what the effect of the Court of Appeals opinion would be, but let's assume it does not bar me collaterally, the issue at the time will be whether the defense that this is not a new drug and therefore no N.D.A. must be in effect will be raised. Your Honor will then have to decide in face whether Ritonic is a new or old drug. On that issue, your Honor, you will have to determine

whether there is general recognition of safety and efficacy, the exact issue which I am suggesting to your Honor to decide now. Now, if you [31] are prepared to say that you would be in a position jurisdiction-wise to decide it in a seizure action, then I would suggest to your Honor that other than the discretion portion, which I will pass for the moment, the question of jurisdiction remains the same as the declaratory judgment entry.

The COURT. I get your argument. What do you have to say?

Mr. ANDERSON. In response to that last point, your Honor, I have only this to say: Mr. Szuch asks rhetorically what is the difference between a seizure action as this action now. The answer is, in the posture of this case, that we are at the end of a lengthy administrative process which Congress has mandated for the review of new drug applications. Congress said, "First you go to the agency and you have your hearing and you establish your record and then you go to the Court of Appeals and you review the record." In the posture of seizure cases, however, there is no new drug application involved. We are at the outset of the matter, the agency has encountered a substance on the market, has determined that the claims made for it are not justified by general recognition of safety and efficacy and has moved by motion for an order of the Court to detain the article. A totally different regulatory posture, your Honor, not at all like what is here.

[32] As your Honor has indicated in that situation, clearly you have jurisdiction. Clearly, you have not only the opportunity but the obligation to determine whether or not the agency has proceeded properly. This is not the case now.

The COURT. Don't you think that I might have jurisdiction in this case, under the Declaratory Judgment Act?

Mr. ANDERSON. I am not prepared to say that you do, your Honor, in the face of those Courts which have spoken on the issue.

Your Honor is right that this is new law, and the decisions are only now coming down, as evidenced by our brief. I can only tell you that what Judge Fulham has told us in Lemon, and what Judge Northrup has told us in Hinson, Westcott and Dunning is that these issues are properly raised before the agency, for review by the Court of Appeals. They recognize the lack of facilities and the lack of necessity for the District Court

to intervene and hold a separate trial on the issue, observing that there was available perfectly adequate review in the Court of Appeals on all legal and factual issues. So to that extent, based on what has been said by the District Court, I think that your Honor does not have justification for asserting what is discretionary jurisdiction.

The COURT. Well, I am going to decide this by granting the defendant's motion for dismissal of the action. I [33] do not think in the present posture of this case that I do have jurisdiction, but even assuming that I did have jurisdiction under the Declaratory Judgment Act I would exercise my discretion and dismiss the action.

That will be the decision of the Court. There will be no costs allowed. Submit an appropriate order, and then, Mr. Szuch, that will give you an opportunity to take the train and go to Philadelphia.

United States District Court for the District of New Jersey

[Caption omitted]

#### ORDER

This matter being opened to the Court by Frederick B. Lacey, United States Attorney for the District of New Jersey (Richard M. Langway, Assistant U.S. Attorney and Robert N. Anderson, Esq. appearing) in the presence of Pitney, Hardin & Kipp, attorneys for plaintiff (Clyde A. Szuch, Esq. appearing) on a motion of defendants for an order of dismissal for lack of jurisdiction of the subject matter or in the alternative for summary judgment of dismissal; and the Court having considered the pleadings and memoranda of law filed in support of and in opposition to the motion; and the Court having heard and considered the arguments of counsel and having rendered its decision in open court on January 11, 1971; and good cause having been shown

IT IS ON THIS 10th DAY OF MARCH, 1971

ORDERED that defendants' motion for dismissal of the complaint for lack of jurisdiction over the subject matter be and the same is hereby granted and the complaint is dismissed, without costs.

ANTHONY T. AUGELLI, U.S.D.J.

United States Court of Appeals For the Third Circuit

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No. 71-1512

CIBA CORPORATION, A CORPORATION OF THE STATE OF DELAWARE,  
APPELLANT

vs.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION &  
WELFARE AND DR. CHARLES C. EDWARDS, COMMISSIONER OF  
FOOD AND DRUGS

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Appeal From the United States District Court for the District  
of New Jersey

Argued April 11, 1972

Before HASTIE, VAN DUSEN and ALDISERT, *Circuit Judges*

OPINION OF THE COURT

[Filed June 5, 1972]

PER CURIAM:

Ciba Corporation has taken this appeal from an order of the District Court for the District of New Jersey dismissing a complaint in which Ciba sought a declaratory determination that its drug product, Ritonic Capsules, is exempt from the requirement of 1962 amendments of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355, that new drugs be excluded from the market unless proven effective as claimed for them. The complaint also sought an injunction against the implementation of an administrative order, entered by the Commissioner of Food and Drugs after notice and opportunity for an evidentiary hearing, that withdrew approval of the drug upon the basis of a finding that the manufacturer's claims as to its effectiveness were unproven. On appeal, the Court of Appeals for the Second Circuit has affirmed that order. *Ciba-Geigy Corp. v. Richardson*,

1971, 446 F.2d 466. That affirmance occurred after the district court had dismissed the present suit and is subject to review by the Supreme Court.

The appellant's basic position seems to be that neither the Commissioner in an administrative proceeding under § 355(e) to determine whether lack of effectiveness as claimed makes a drug unmarketable, nor a court of appeals in reviewing the administrative decision, has jurisdiction to decide as to threshold question whether the product in controversy is a "new drug" within the meaning of the statute, § 355, that covers "new drug" applications and administrative proceedings pursuant thereto. We find no merit in that argument. Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.

In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. That determination is reviewable by the Supreme Court. It is neither necessary nor appropriate that the District Court for the District of New Jersey entertain a separate suit by the loser in the administrative proceedings and in the direct appeal therefrom for a redetermination of the same question.

The judgment will be affirmed.

In the United States Court of Appeals for the Third Circuit

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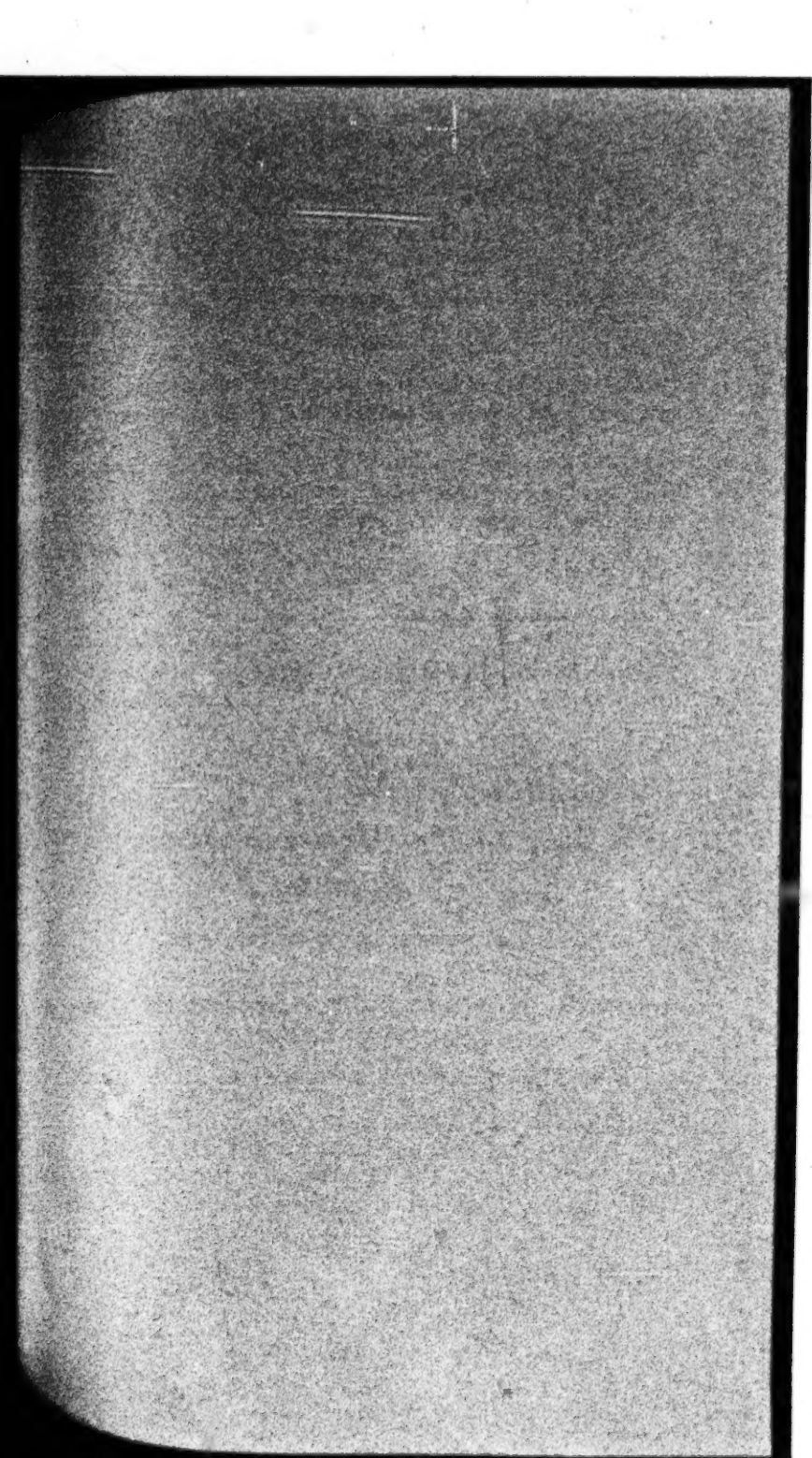
No. 71-1512

CIBA CORPORATION, APPELLANT,

vs.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION & WELFARE AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS.







(D. C. Civil Action No. 1210-70)

ON APPEAL FROM THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEYPresent: HASTIE, VAN DUSEN and ALDISERT, *Circuit Judges.*

## JUDGMENT

This cause came on to be heard on the record from the United States District Court for the District of New Jersey and was argued by counsel.

On consideration whereof, it is now here ordered and adjudged by this Court that the judgment of the said District Court, filed March 10, 1971, be, and the same is hereby affirmed, with costs taxed against appellant.

Attest:

(S) THOMAS F. QUINN, *Clerk.*

June 5, 1972

Certified as a true copy and issued in lieu of a formal mandate on June 27, 1972.

Test:

(S) THOMAS F. QUINN  
*Clerk, United States Court of  
Appeals For The Third Circuit.*

In the Supreme Court of the United States

No. 72-528

CIBA CORPORATION, PETITIONER,

v.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION  
AND WELFARE, ET AL.

ORDER ALLOWING CERTIORARI. FILED JANUARY 8, 1973

The petition herein for a writ of certiorari to the United States Court of Appeals for the Third Circuit is granted. The case is consolidated with Nos. 72-394, 72-414, 72-555 and 72-666, and a total of three hours is allotted for oral argument.

## United States Court of Appeals for the Fourth Circuit

(Civil No. 71-1243)

BENTEX PHARMACEUTICALS, INC., ET AL., APPELLANTS

v.

ELLIOT L. RICHARDSON, ET AL., APPELLEES

## RELEVANT DOCKET ENTRIES

*Date*

- 3/11/71 Record on appeal in one volume (Volume I) filed and appeal docketed.
- 3/11/71 Exhibits in one envelope received from the Clerk of the District Court at Columbia, South Carolina.
- 3/16/71 Appearance for the appellants filed and entered.
- 3/19/71 Appellants' designation of the portions of the record to be included in the appendix and statement of issue filed.
- 4/15/71 Appearance for the appellees filed and entered.
- 4/20/71 Brief for appellants filed. 25 copies.
- 5/19/71 Appellee's motion for enlargement of time to file its brief to June 30, 1971, filed. Motion granted.
- 7/ 6/71 Brief and appendix for appellees filed. 25 copies.
- 7/ 8/71 Appellants' motion for enlargement of time to file reply brief to July 31, 1971, filed. Motion granted.
- 7/26/71 Motion for enlargement of time to file appellant's reply brief to 8-15-71 filed. Motion granted.
- 8/13/71 Reply brief for appellants filed. 25 copies.
- 11/16/71 Notice of oral argument mailed to Townes, Abrams, Epstein, Goodrich, and Anderson.
- 12/ 8/71 Appearance for appellee filed and entered.
- 12/ 8/71 Cause argued before Winter, Russell and Field, Circuit Judges, and submitted.
- 12/17/71 Above record on appeal with tape mailed to Judge Russell.

- Date*
- 5/12/72 Record on appeal in one volume and exhibits in one envelope received from Judge Russell.
  - 5/23/72 Opinion filed.
  - 5/23/72 Opinion and Clerk's Memorandum mailed to counsel of record. (Mailed to Townes, Abrams and Epstein.) Copy of opinion mailed to the Clerk of the District Court at Greenville, South Carolina.
  - 5/23/72 Judgment of the district court remanded with directions. Judgment filed.
  - 6/14/72 Certified copy of the judgment and printed copy of the opinion transmitted to the Clerk of the District Court at Columbia, S.C.
  - 6/14/72 Record on appeal in one volume and exhibits in one envelope returned to the Clerk of the District Court at Columbia, S.C.
  - 10/10/72 Notice evidencing the filing petition for certiorari in the Supreme Court October 5, 1972 filed. (No. 72-555)
  - 1/12/73 Order of the Supreme Court granting certiorari January 8, 1973 filed.
  - 2/ 2/73 Record on appeal in one volume and exhibits in one envelope received from the Clerk of the District Court at Columbia, South Carolina.
  - 2/ 2/73 Certified record in two volumes and exhibits in one envelope transmitted to the Clerk of the Supreme Court.

In the United States District Court for the District of  
South Carolina

GREENVILLE DIVISION

(Complaint C/A No. 70-1001)

O'NEAL, JONES & FELDMAN, INC., BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE

BLAINE COMPANY, BROWN PHARMACEUTICAL Co., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL Co., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL Co., W. E. BOODY & Co., PLAINTIFFS

vs.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, DEFENDANTS.

The plaintiffs, complaining of the defendants, would respectfully show the Court:

#### I.

The Food and Drug Administration is an agency of the United States of America under the Department of Health, Education and Welfare. Elliot P. Richardson is the Secretary of the Department of Health, Education and Welfare, and Charles C. Edwards is the Commissioner of the Food and Drug Administration, and they are made parties to this action in their said representative capacities.

#### II.

One of the plaintiffs, Pisgah Pharmaceuticals, Inc., is a South Carolina Corporation, having its principal place of business in Greenville, South Carolina, a place within the physical jurisdiction of this Court.

#### III.

The plaintiffs are corporations a part of whose business involves the manufacture and/or sale and distribution of drugs in interstate commerce containing pentylenetetrazol and/or nicotinic acid; except the plaintiff, O'Neal, Jones & Feldman, Inc., and that plaintiff contemplates engaging in said business.

#### IV.

The sale of these several drugs in interstate commerce is regulated by Title 21, Chapter 9 of the United States Code, called the Federal Food, Drug and Cosmetic Act.

## V.

The Food and Drug Administration is granted and charged with the exercise of administrative and regulatory powers and duties under said act.

## VI.

This action is brought under Title 5, Chapter 7 of the United States Code.

## VII.

The Food and Drug Administration published in the FEDERAL REGISTER, Vol. 35, No. 98, dated Wednesday, May 20, 1970, on page 7749 a notice entitled "Pentylentetrazol-Containing Drugs." The contents of the notice are fully set forth in Exhibit A of this complaint, and contents of said exhibit are incorporated by reference as part of the allegations of this paragraph.

## VIII.

This notice was issued in proceedings instituted for the withdrawal of approval of new-drug applications for Geroniazol Injection (NDA 11-742) and Nicozol with Reserpine tablets (NDA 10-508), containing the ingredients and proportions as set forth in said notice. These new-drug applications were held by Phillips Roxane Laboratories, Division of Phillips Roxane, Inc. and Nysco Laboratories, Inc. Hart Laboratories, holder of NDA 11-347, Nicozol with Reserpine Tablets, was a party to said proceedings.

## IX.

The proposed order of which notice was given was to the effect that approval of the above new-drug applications would be withdrawn "on the grounds that there is a lack of substantial evidence that these drugs have the effect they purport to have under the conditions of use prescribed, recommended, or suggested in their labeling."

## X.

The said notice contained this language:

Promulgation of the purposed order will cause any drug for human use containing the same active sub-

stances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

#### XI.

The orders proposed by the notice were issued on September 3, 1970 at CFR 2:120. Said orders are fully set forth as Exhibit B of this complaint and the contents of said exhibit are incorporated by reference as part of the allegations of this paragraph.

#### XII.

The plaintiffs are informed and believe that the Food and Drug Administration contemplates and is about to institute such regulatory proceedings against the plaintiffs.

#### XIII.

Title 21, Section 321 (p) (1) United States Code, defines the term "new drug" as follows:

(p) The term 'new drug' means—(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that it is not generally recognized, among experts qualified by the scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed a 'new drug' if at any time prior to the enactment of this chapter it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use. . . .

#### XIV.

The drugs, pentylenetetrazol and nicotinic acid, were subject to the Food and Drug Act of June 30, 1906, as amended, prior to the enactment of said chapter.

## XV.

The enactment of said chapter was October 9, 1962.

## XVI.

The manufacture and distribution of said drugs in interstate commerce by the plaintiffs has been under the exception (called the "grandfather clause") provided for in Title 21, Section 321 (p) (1) as quoted above, and/or under the claim that said drugs are not "new drugs" as therein defined, and not under any new-drug application.

## XVII.

None of the plaintiffs was a party to the proceedings resulting in the notice and orders contained in Exhibits A and B of this complaint.

## XVIII.

The plaintiffs are informed and believe that the provisions of the notice alleged in Paragraph X, and the policy, intention, and decision of the Food and Drug Administration as therein enunciated, are invalid and nugatory for the reasons alleged herein:

(1) The declaration that any drug on the market containing the "same active substances" is a "new drug" cannot lawfully be made in a proceeding brought for the withdrawal of approval of one or more specified new-drug applications under Section 355, Title 21.

(2) Said declaration cannot lawfully be made on the basis that there is "a lack of substantial evidence that these drugs have the effect they purport to have under the conditions of use prescribed, recommended, or suggested in their labeling", but only on the basis that such drugs are "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .", the latter being the definition of a new drug (other than a drug allowed under the "grandfather clause").

(3) Said declaration cannot lawfully be made in a degree of generality which makes such declaration applicable regardless of the total composition of any drug containing "the same active substances", and of the "conditions prescribed, recommended or suggested in the labeling thereof."

(4) Said declaration cannot lawfully be made so as to ignore, override and set aside the provisions of the "grandfather clause".

(5) Said declaration cannot lawfully be made so as to bind persons not parties to the proceedings and not interested in the specific compounds, "Geroniazol Injection", "Nicozol with Reserpine" and "Nicozol with Reserpine Tablets" covered by NDA 11-742, NDA 10-508 and NDA 11-347.

## XIX.

The reasons why such declaration cannot lawfully be made as alleged above are:

(1) Such declaration violates and is not in accordance with the Statutory Law.

(2) The promulgation of the declaration in the proceedings had and held is in excess of the authority of the Food and Drug Administration as granted by Statute.

(3) The promulgation of the declaration in the proceedings had and held is in violation of due process of law in that the Food and Drug Administration failed to follow statutory authority and to afford reasonable, proper and orderly procedures for the determination of the issues, with adequate notice to all affected, and is without observance of procedure required by law.

(4) The promulgation of the declaration in the proceedings had and held is unwarranted by the facts as found and reported therein.

## XX.

The plaintiffs are informed and believe that the action of the Food and Drug Administration is a final agency action for which there is no other adequate remedy in a Court.



## XXI.

If the asserted position of the Food and Drug Administration is valid, continued manufacture and sale in interstate commerce of said drugs would be in violation of Title 21, Sec. 331, said drugs may be seized under Title 21, Sec. 334, and the plaintiffs and their agents may be subject to criminal penalties under Title 21, Sec. 333.

## XXII

The said declaration forces the plaintiffs either to abandon their business of manufacturing and/or selling said drugs, thereby causing them irreparable loss, or to risk the penalties which may be involved should the declaration complained of be found lawful.

## XXIII

Each of the plaintiffs has a substantial economic interest in the manufacture and/or sale of these drugs, and will be substantially and irreparably injured if the provisions of the notice set forth in Paragraph X above are enforced.

## XXIV

The said drugs are nowhere asserted by the Food and Drug Administration to be harmful.

## XXV

The plaintiffs are entitled to a judgment declaring that the declaration herein complained of is invalid. The plaintiffs are further entitled to an order, pending such declaration, enjoining the Food and Drug Administration from implementing said declaration as against the plaintiffs until the Court decides whether such declaration is valid.

WHEREFORE the plaintiffs pray:

- (1) That the Court determine the scope, validity and enforceability of the declaration alleged in Paragraph X;
- (2) That the Court declare the said declaration to be invalid;

(3) That the Court restrain regulatory proceedings taken pursuant to such declaration until the validity thereof is determined, and that it grant such relief pendente lite;

(4) That the Court grant such further relief as may be proper.

ABRAMS, BOWEN AND TOWNES,  
By GEORGE F. TOWNES,  
*Attorney at Law,*  
*P. O. Box 10128 F. S.,*  
*Greenville, S.C. 29603.*

By SOL E. ABRAMS,  
*Attorney at Law,*  
*P. O. Box 10128 F. S.,*  
*Greenville, S.C. 29603.*

Greenville, South Carolina  
November 27, 1970

34 F.R. 13673 (August 26, 1969)

*Food and Drug Administration*

CERTAIN COMBINATION PREPARATIONS CONTAINING  
PENTYLENETETRAZOL

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Geroniazol Injection; contains 100 milligrams of pentylenetetrazol and 50 milligrams of nicotinic acid, as sodium nicotinate, per milliliter; by Philips Roxane Laboratories, Division of Philips Roxane, Inc., 330 Oak Street, Columbus, Ohio 43216 (NDA 11-742).

2. Nicozol with Reserpine Tablets; contains 100 milligrams of pentylenetetrazol, 50 milligrams of nicotinic acid, and 0.25 milligram of reserpine per tablet; Nysco Laboratories, Inc., 34-24 Vernon Boulevard, Long Island City, N.Y. 11106 (NDA 10-508).

The Food and Drug Administration concludes there is a lack of substantial evidence that these drugs will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling, as follows:

1. Geroniazol Injection—for use in the treatment of senile confusion, senile depression, senile psychosis, senile fatigue, and senile debilitation.

2. Nicozol with Resperine Tablets—for use in senile psychoses and psychoneuroses, when anxiety and nervous tension are present; and relief of dizzy spells, mental confusion, mild behavioral disorders, irritability, and functional memory defects in elderly patients, in the absence of more serious emotional and psychiatric disturbances.

Accordingly, the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the above-listed new-drug applications.

Prior to initiating such action, however, the Commissioner invites the holders of new-drug applications for these drugs and any interested person who might be adversely affected by their removal from the market, to submit any pertinent data bearing on the proposal within 30 days after publication hereof in the Federal Register. To be considered acceptable for review, the material must be well-organized and consist of adequate and well-controlled studies bearing on the efficacy of the products and must not have been previously submitted.

This announcement of the proposed action and implementation of the NAS-NRC report for these drugs is made to give notice to persons who might be adversely affected by their withdrawal from the market. Promulgation of an order withdrawing approval of the new-drug applications will cause any such drug on the market to be a new drug for which an approved new-drug application is not in effect and will make it subject to regulatory action.

The above-named holders of the subject new-drug applications have been mailed a copy of the NAS-NRC reports and any interested person may obtain a copy on request from the office named below.

Communications forwarded in response to this announcement should refer to "DESI 10508," should be directed to the following appropriate office, and should be addressed to the

Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204:

Requests for NAS-NRC report: Press Relations Office (CE-300). Comments or data regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (MD-16), Bureau of Medicine.

This announcement is issued pursuant to the provisions of the Federal Food Drug and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: August 12, 1969.

HERBERT L. LEY, Jr.,  
*Commissioner of Food and Drugs.*

[F.R. Doc. 69-10107; Filed, Aug. 25, 1969; 8:45 a.m.]

35 F.R. 7749 (May 20, 1970)

*Food and Drug Administration*

[Docket No. FDC-D-177; NDA No. 11-742 et al.]

**PENTYLENETETRAZOL-CONTAINING DRUGS**

**Drugs for Human Use; Drug Efficacy Study Implementation;  
Notice of Opportunity for Hearing**

In an announcement (DESI 10508) published in the Federal Register of August 26, 1969 (34 F.R. 13673), Philips Roxane Laboratories, Division of Philips Roxane, Inc., 330 Oak Street, Columbus, Ohio 43216, and Nysco Laboratories, Inc., 34-24 Vernon Boulevard, Long Island City, N.Y. 11106, the holders of the new-drug applications for Geroniazol Injection (NDA 11-742) containing per milliliter 100 milligrams pentylenetetrozol and 50 milligrams of nicotinic acid, as sodium nicotinate; and Nicozol with Reserpine tablets (NDA 10-508) containing 100 milligrams of pentylenetetrozol, 50 milligrams of nicotinic acid, and 0.25 milligram of reserpine per tablet, respectively, as well as any other interested person, were invited to submit pertinent data bearing on the announced intention to initiate proceedings to withdraw approval of the new-drug applications.

On December 18, 1969, Philips Roxane submitted material for consideration. The material was reviewed and considered together with other available information, does not provide substantial evidence of effectiveness of the drug for the recommended uses in man.

Therefore, notice is hereby given to Philips Roxane Laboratories, Division of Philips Roxane, Inc., and Nysco Laboratories, Inc., and to any other interested person who may be adversely affected by such action, including Hart Laboratories, Station Square One, Paoli, Pa. 19301, holder of NDA 11-347 (Nicozol, with Reserpine Tablets), originally applied for by Drug Specialties, Inc., Winston-Salem, N.C., that the Commissioner of Food and Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the listed new-drug applications and all amendments and supplements thereto on the grounds that there is a lack of substantial evidence that these drugs have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling.

In addition to the new-drug applications listed above, a number of other applications provide for preparations containing pentylenetetrazol for systemic use in humans. Their holders have voluntarily requested withdrawal of approval of those applications, thereby waiving opportunity for hearing; therefore, they are not listed in this notice.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the applicant, and any interested person who would be adversely affected by an order withdrawing such approval, an opportunity for a hearing to show why approval of any new-drug application listed herein should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office

of the General Counsel, Room 6-62, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing;  
or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the new-drug applications. Failure of such persons to file such a written appearance of election within said 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion concerning a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing, they must file a written appearance requesting the hearing, giving the reasons why the approval of the new-drug application should not be withdrawn together with a well-organized and full-factual analysis of the clinical and other investigational data they are prepared to prove in support of their opposition. The request must set forth specific facts showing there is a genuine and substantial issue of fact that requires a hearing. If the hearing is requested and justified by the response to this notice, the issues will be defined, a hearing examiner will be appointed, and he shall issue a written notice of the time and place at which the hearing will commence.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-53, as amended; 21 U.S.C. 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: May 12, 1970.

SAM D. FINE,  
*Acting Associate Commissioner for Compliance.*

[F.R. Doc. 70-6175; Filed, May 19, 1970; 8:45 a.m.]

35 F.R. 14412 (September 12, 1970)

*Food and Drug Administration*

[Docket No. FDC-D-177; NDA 11-742, etc.]

**NYSCO LABORATORIES, INC., AND HART LABORATORIES****Pentylenetetrazol-Containing Drugs for Human Use; Notice of Withdrawal of Approval of New-Drug Application**

On May 20, 1970, there was published in the **FEDERAL REGISTER** (35 F.R. 7749) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications listed therein on the ground that there is a lack of substantial evidence that these drugs have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling.

The following firms, listed with their address, respective drug, and new drug application number, have waived opportunity for a hearing on the proposed withdrawal of said new-drug applications in that no response has been received.

NDA No.	Drug name	Applicant's name and address
10-508----	Nicozol with Reserpine tablets.	Nysco Laboratories, Inc., 34-24 Vernon Blvd., Long Island City, N.Y. 11106.
11-347-----	do-----	Hart Laboratories, Station Square 1, Paoli, Pa. 19301.

The Commissioner of Food and Drugs, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, that there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing findings, approval of the above new-drug applications, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document. Outstanding stocks of the affected drugs should be recalled.

Dated: September 3, 1970.

SAM D. FINE,  
*Associate Commissioner for Compliance.*

[F.R. Doc. 70-12141; Filed, Sept. 11, 1970; 8:46 a.m.]

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[Docket No. FDC-D-177; NDA 11-742 etc.]

**PHILIPS ROXANE LABORATORIES**

**Pentylenetetrazol-Containing Drugs for Human Use; Notice of  
Withdrawal of Approval of New-Drug Application**

On May 20, 1970, there was published in the **FEDERAL REGISTER** (35 F.R. 7749) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications listed therein on the ground that there is a lack of substantial evidence that these drugs have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling.

Philips Roxane Laboratories, Division of Philips Roxane, Inc., holder of NDA No. 11-742 for Geroniazol Injection, 330 Oak Street, Columbus, Ohio 43216, filed a letter requested a hearing pursuant to the May 20, 1970, publication, but did not file any data to support such request. The Commissioner of Food and Drugs concludes there are no genuine and substantial issues of fact to justify a hearing (35 F.R. 7250; May 8, 1970).

The Commissioner of Food and Drugs, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds on the basis of new information before him with respect to such drug evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented



to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing findings, approval of the above new-drug application, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document.

Dated: September 3, 1970.

SAM D. FINE,  
*Associate Commissioner for Compliance.*

[F.R. Doc. 70-12142; Filed, Sept. 11, 1970; 8:46 a.m.]

In the United States District Court for the Western District of  
South Carolina

[Caption Omitted]

#### AFFIDAVIT

Barrett Scoville, M.D., being first duly sworn, deposes and says:

1. I am the Deputy Director of the Division of Neuropharmacologic Drug Products, Office of Scientific Evaluation, Bureau of Drugs, United States Food and Drug Administration.

2. In connection with the responsibility of this Agency to decide whether new drugs are safe and effective for use by the public, this office reviews and evaluates scientific evidence concerning the safety and efficacy of neuropharmacologic drugs.

3. Following the 1962 amendments to the Federal Food, Drug and Cosmetic Act, as part of the program to implement the new efficacy provision of the Act, the Food and Drug Administration requested the National Academy of Sciences, National Research Council, to have highly qualified, expert panels of scientists evaluate the efficacy of pentylenetetrazol combination drugs offered for senile psychosis and psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability and functional memory defects. All available evidence including whatever evidence the NDA sponsors submitted pursuant to the request of FDA, was considered by the NAS-

NRC panels. Their evaluation of these drugs was that they were ineffective for the indicated uses (Exhibit A attached). The Food and Drug Administration, thereafter, also reviewed all of the available evidence concerning these drugs, including the NAS-NRC evaluations, and concluded that there was not substantial evidence to demonstrate that they were effective for the indicated uses. Consequently we commenced proceedings to withdraw approval of all existing new drug applications covering such drugs. There were three such NDAs: NDA 11-742 for Geroniazol injection, held by Philips-Roxane Laboratories, NDA 10-308 for Nicozol with Reserpine, held by Nysco Laboratories, which had been taken over as NDA 11-347, for the same drug, by Hart Laboratories.

4. Notice was published in the Federal Register on August 26, 1969 (34 F.R. 13673, Exhibit B, attached) announcing our conclusion concerning these drugs and inviting the NDA sponsors and any other interested persons to submit any other data they had concerning the effectiveness of these drugs. One firm, Philips-Roxane, submitted data, but it was insufficient and did not alter our conclusion. On May 20, 1970 we published a notice in the Federal Register (35 F.R. 7749, Exhibit C attached) which offered and opportunity for a hearing to the sponsors of the NDA's and any interested person who would be adversely affected by withdrawal of approval of the NDA's. Only one firm requested a hearing (Philips-Roxane), but it failed to provide the required documentation to show that a genuine issue existed which required a hearing for resolution. Notice of withdrawal of the existing NDA's for these pentylene-tetrazol combinations was published in the Federal Register on September 12, 1970 (35 F.R. 14412).

5. As part of my official duties I have reviewed the three new drug applications for pentylenetetrazol combinations referred to in paragraph 4, above. Geroniozol is a combination of pentylenetetrazol and nicotinic acid. Nicozol with Reserpine is a combination of pentylenetetrazol, nicotinic acid and reserpine. Both are neuropharmacologic drugs, and are offered for various senile disorders including psychosis, neuropsychosis, fatigue, confusion, debilitation, depression, dizzy spells and other behavioral disorders.

6. Based on my training and experience including my review of the subject new drug applications, my knowledge of the scientific literature, the NAS-NRC evaluation of these drugs, and my professional contacts with other physicians, in this field and on the basis of the information which comes to me in my official capacity as Deputy Director of the Division of Neuropharmacologic Drug Products, Office of Scientific Evaluation, Bureau of Drugs, United States Food and Drug Administration, it is my opinion that pentylenetetrazol, alone, or in combination with nicotinic acid, or nicotinic acid and reserpine, is not now, and never has been, generally recognized, by qualified experts, as both safe and effective for the treatment of senile psychosis or psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability, or functional memory defects.

BARRETT SCOVILLE, M.D.

Subscribed and sworn to before me this \_\_\_\_\_ day of \_\_\_\_\_, 1970.

\_\_\_\_\_  
Notary Public.

*National Academy of Sciences—National Research  
Council—Division of Medical Sciences*

**DRUG EFFICACY STUDY**

*Form A*

(To be submitted in duplicate by applicant)

1. NDA Number: 10-508 E-01
2. Date Originally Approved: June 7, 1957
3. Rx X OTC —
4. Brand Name: Nicozol with Reserpine
5. Applicant's Name: Nysco Laboratories, Inc.  
and Address: 3424 Vernon Boulevard, Long Island City,  
N.Y.
6. Quantitative Formula:

Established (Non-Proprietary) Name of Active Ingredients (In order shown on label):	Amount (per tablet, per ml., etc.)
Pentylenetetrazol .....	100 mg
Nicotinic Acid .....	50 mg
Reserpine .....	0.25 mg

7. Dosage Form (tablets, etc.): Tablets
8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral
9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).
10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).) We have no additional information than that submitted with our original application.
11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.
12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white). None

### NICOZOL

#### WITH RESERPINE

#### For Senile Psychoses With Agitation

**WHAT IT IS:** Pale buff, scored tablets with engraved square. Each tablet contains:

Pentylenetetrazol—100 mg.

Nicotinic Acid—50 mg.

Reserpine—0.25 mg.

Combines the tranquilizing action of reserpine with the cerebral stimulation (analeptic) and improved behavior produced by Nicozol (pentylenetetrazol and nicotinic acid).

**THERAPEUTIC RESULTS:** In elderly patients behavior, personal habits, sociability, memory, appearance and general activity are improved. Anxiety and nervous tension are relieved. Other benefits include relief of dizzy spells, mental confusion and irritability.

**INDICATIONS:** Senile psychoses and psychoneuroses, when anxiety and nervous tension are present. Relief of dizzy spells, mental confusion, mild behavioral disorders, irritability and functional memory defects in elderly patients, in the absence of more serious emotional and psychiatric disturbances. Not recommended in the treatment of hypertension.

**DOSAGE:** 1 tablet 3 times a day; in severe cases, 2 tablets 3 times a day.

**CAUTION:** Federal law prohibits dispensing without prescription.

**CONTRAINDICATIONS:** Should not be given to patients within 3 days prior to use of electroconvulsive treatment or those receiving intravenous injections of pentylenetetrazol. Discontinue medication in the event that muscular twitchings or clonic convulsions occur. Dosage should be reduced or discontinued if nasal congestion, nausea, vomiting, diarrhea or mental depression occur. Mental depression and peptic ulcer are relative contraindications to the use of reserpine. In such cases NICOZOL with RESERPINE should be used with caution.

The flush experienced by sensitive individuals is not detrimental and is part of the nicotinic acid therapy. There may be an occasional case of pruritus due to nicotinic acid.

**SUPPLIED:** Bottles of 100, 1000 tablets.

February 1962

**HART LABORATORIES**

*Division of A. J. Parker Company, Winston-Salem, N.C.*

NICOZOL  
NDA 10508  
LOG 2660

#### PANEL ON PSYCHIATRIC DRUGS

##### INDICATIONS

*1. Nicozol (reserpine) is indicated as useful in senile psychoses, when anxiety and nervous tension are present*

**EVALUATION:** Ineffective.

**COMMENTS:** Nicozol with Reserpine is a combination of pentylenetetrazol and nicotinic acid with reserpine. Pentylene-

tetrazol and nicotinic acid form the combination known as Geroniazol, which has been evaluated as "Ineffective" by the Panel in the treatment of senile confusion, with the following comment:

(From DES Evaluation of Geroniazol, NDA 11742, Log 653). Many uncontrolled studies claim efficacy for oral Metrazol, and a few for nicotinic acid in geriatric organic psychoses and confusional states. One small controlled study of i.v. medication shows a trend favoring the oral form over the i.v., and the i.v. over placebo. Two controlled studies that are small, with rather weak and inappropriate criteria and methods for evaluating clinical improvement, favor Metrazol (1,3). The only study of i.v. medication in nonsenile depression shows little efficacy (three of 18 improved). There is no evidence presented on treatment of fatigue or psychosis in other than senile conditions.

#### DOCUMENTATION:

1. Mead, S., E. E. Mueller, E. P. Mason, T. Kheim, and W. B. Kountz. A study of the effects of oral administration of metrazol in old individuals. *J. Geront.* 8:472-476, 1953.
2. Pacella, B. L., J. Doltolo, and R. R. Cerulli. Subconvulsive metrazol therapy. *J. Nerv. Ment. Dis.* 117:50-54, 1953.
3. Swensen, W. M., and B. P. Grimes. Oral use of metrazol in senile patients. *Geriatrics* 8:99-101, 1953.

In general, the use of reserpine in the treatment of major psychoses has been established. Dosages in the treatment of psychoses are rarely less than 1 mg/day, whereas those used in the treatment of hypertension rarely exceed 1 mg/day.

With the advent of the phenothiazines, the use of reserpine as an antipsychotic medication has declined, although it still has a rational basis in antipsychotic therapy. Many studies show reserpine to be more effective than placebo in the treatment of psychoses.

The Panel accordingly evaluated the combination known as Nicozol with Reserpine as "Ineffective" for this indication. In addition, the Panel finds the wording of the indication imprecise and suggests the deletion of the phrase "nervous tension."

*II. Nicozol (reserpine) is indicated as useful in psychoneuroses, when anxiety and nervous tension are present*

**EVALUATION: Ineffective.**

**COMMENTS:** The Panel feels that the efficacy of reserpine and reserpine compounds in the treatment of anxiety has not been established. Since the introduction of reserpine, a number of representatives of several classes of drugs with more conventional sedative properties have been introduced and found to be effective—to the extent that drugs are—in the treatment of anxiety. Although reserpine exerts some effect in calming the anxious patient, the concomitant risk of reserpine's depression-producing effect should be noted. It is the Panel's judgment that—in the general practice of psychiatry today—the use of reserpine as an antianxiety agent is obsolete.

The treatment of anxiety with drugs is complicated by many non-drug factors (5), such as the personality of the patient, his relationship to the physician, and innumerable and varying social and environmental factors. Claims for the effectiveness of reserpine and reserpine compounds in producing sedation and reducing tension represent as yet poorly differentiated general effects of calming and tranquilization, specific definitions are not supported in the literature cited by the manufacturers. In addition, the literature is scanty and poorly documented, relying on predominantly uncontrolled studies.

See also Comments for Indication I.

Because there is no evidence presented for the efficacy of nicotinic acid and pentylenetetrazol as antianxiety agents, the Panel evaluates the combination "Ineffective" for this indication. In addition, the Panel finds the wording of the indication imprecise and suggests the deletion of the phrase "nervous tension."

**DOCUMENTATION:**

1. Davis, J. M. Efficacy of tranquilizing and antidepressant drugs. *Arch. Gen. Psychiat.* (Chicago) 13:552-572, 1965.

2. Ferguson, R. S. A. clinical trial of reserpine in the treatment of anxiety. *J. Ment. Sci.* 102:30-42, 1956.

3. Hauck, P., H. Phillips, and R. Armstrong. The effects of reserpine on psychotic patients of varying degrees of illness: a pilot study. *J. Clin. Psychol.* 13:188-190, 1957.

4. Lemieux, G. A. Davignon, and J. Genest. Depressive states during rauwolfia therapy for arterial hypertension; a report of 30 cases. *Canad. Med. Assoc. J.* 74:522-526, 1956.

5. Rickels, K., Ed. Non-specific factors in drug therapy. *Non-specific Factors in Drug Therapy of Neurotic Patients*. Springfield: Charles C. Thomas, 1968.

#### GENERAL COMMENTS

The Panel finds the following statement in the package insert vague and too general and suggests its deletion from the package insert:

Relief of dizzy spells, mental confusion, mild behavioral disorders, irritability and functional memory defects in elderly patients, in the absence of more serious emotional and psychiatric disturbances.

Approved by \_\_\_\_\_,

*Chairman.*

#### DIVISION OF MEDICAL SCIENCES

#### DRUG EFFICACY STUDY

#### *Form A*

(To be submitted in duplicate by applicant)

1. NDA Number: 11-742 E-01 2. Date Originally Approved: 1-19-59 1315 3. Rx X OTC.
4. Brand Name: GERONIAZOL Injection
5. Applicant's Name: Philips Roxane Laboratories, Division of Philips Roxane, Inc.  
and Address 330 Oak Street, Columbus, Ohio 43216
6. Quantitative Formula

Amount (per  
tablet, per  
ml., etc.)

Established (Non-Proprietary) Name of Active Ingredients  
(in order shown on label) : Each ml. contains :

Pentylentetrazol .....	100 mg.
Nicotinic Acid (as the sodium salt) .....	50 mg.

7. Dosage Form (tablets, etc.) Sterile injection



8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Subcutaneously, intramuscularly, intravenously.
9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).
10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)  
NONE
11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.
12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).  
NONE

Similar results were obtained with parenterally administered nicotinic acid by Gregory (10), Washburn (11) and Moore (12) in senile and arteriosclerotic psychoses. The importance of early treatment is again stressed (10).

In view of the documented success of both pentylenetetrazol and nicotinic acid parenterally administered, their presentation together in a single injectable dosage form is highly rational and should produce a greater mutual enhancement of their respective therapeutic actions and speedier response than demonstrated by their concurrent oral administration. The supplementation of oral therapy by the parenteral dosage form can be expected to produce greater and more rapid therapeutic success in the treatment of senile confusion, depression, psychosis, fatigue and debilitation.

#### CONTRAINDICATIONS

In patients with a history of epilepsy, hemorrhagic pulmonary tuberculosis, acute brain injury and weakness of the bony system.

## PRECAUTIONS

Intravenous injection should be reserved for severe cases or those not responding to subcutaneous or intramuscular doses, and only administered with the patient in bed or lying down. Dosage should not be repeated in less than 2 to 3 hours. The patient should not be released in less than 20 minutes after injection. Intravenous dosage above 2 cc., especially if rapidly administered may produce a convulsion and unconsciousness lasting from 5 to 15 seconds. Overdosage is indicated by a slight twitching of the face and body or blacking out of the patient, but effects are dissipated in a short time. When necessary, convulsions may be readily arrested by intravenous barbiturates.

## DOSAGE AND ADMINISTRATION

Subcutaneously: 1 cc. Intramuscularly; 1 to 2 cc. Intravenously; initially 1 cc. *injected slowly*. If no reaction (other than flushing) occurs, increase on subsequent days by increments to 2 cc.

Best results are obtained by administering 2 or 3 times weekly for several weeks, then once a week for 2 to 3 months, depending on the response of the patient.

## SUPPLIED

AM-175, 10cc. Multiple Dose Vial

## References

- (1) Levy, S.; J.A.M.A., 153:1260, 1953.
- (2) Thompson, J. and Proctor, R. C.; No. Carolina M. J. 51:596, 1954.
- (3) Seidel, H. et al; J. Am. Geriatrics Soc., 1:280, 1953.
- (4) Sal y Rosas, F.; through J.A.M.A., 119:378, 1942.
- (5) Hirschmann, J.; Deutsche Med. Wehnschr., 74:513, 1949.
- (6) Leroy, A.; J. belge neruol, Psychiat., 38:613, 1938.
- (7) Lieberman, A. L.; Geriatrics, 9:125, 1954.
- (8) Pacella, B. et al; J. Nerv. & Ment. Dis. 117:50, 1953.
- (9) Lieberman, A. L. et al; Geriatrics, 9:371, 1954.
- (10) Gregory, I.; Am. J. Psychiat., 108:838, 1952.
- (11) Washburne; Ann. Int. Med., 32:261, 1950.

- (12) Moore, D. F. et al; J. Clin. & Exper. Psychopath, 12:249, 1951.

PHILIPS ROXANE LABORATORIES

*Division of Philips Roxane, Inc.  
Columbus, Ohio, U.S.A.*

GERONIAZOL INJECTABLE

COMPOSITION

Each cc. contains:

Pentylenetetrazol -----	100 mg.
Nicotinic Acid (as the sodium salt) -----	50 mg.
Benzyl Alcohol (preservative) -----	1.5%

INDICATIONS

In the treatment of senile confusion, depression, psychosis, fatigue and debilitation.

Geroniazol injectable presents in parenteral form the therapy originally introduced by Levy (1) and since confirmed by Thompson (2), Seidel (3) and others, as an effective oral treatment in senile confusion and mental deterioration. The pharmacological basis of this therapy is the combatting of cerebral anoxia through the respiratory and circulatory stimulant actions of pentylenetetrazol and the peripheral vasodilator action of nicotinic acid.

Ample evidence is available (4-12), indicating that a more rapid and profound response in these and other conditions can be expected by the parenteral administration of this therapy alone, or in conjunction with oral administration.

Saly Rosas (4), Hirschmann (5) and Leroy (6) reported that injections of pentylenetetrazol in moderate (sub-convulsive) dosage were extraordinarily helpful in the treatment of anxiety neuroses, endogenous depression, and melancholia, particularly in early cases, Lieberman (7,9) and Pacella (8) obtained highly encouraging results from the employment of i.v. injections of sub-convulsive doses of pentylenetetrazol in geriatric patients with arteriosclerotic mental changes, with greatest success being found in early cases. The response was much more rapid than that obtained with oral pentylenetetrazol (9).

This drug has been evaluated by the following Panels:

1. Panel on Psychiatric Drugs
2. Panel on Drugs Used in Anesthesiology
3. Panel on Drugs Used in Respiratory Disturbances

Evaluations follow:

### PANEL ON PSYCHIATRIC DRUGS

#### INDICATIONS

- I. Geroniazol Injection is used in the treatment of senile confusion*

**EVALUATION:** Ineffective.

**COMMENTS:** Many uncontrolled studies claim efficacy for oral Metrazol, and a few for nicotinic acid in geriatric organic psychoses and confusional states. One small controlled study of i.v. medication shows a trend favoring the oral form over the i.v., and the i.v. over placebo. Two controlled studies that are small, with rather weak and inappropriate criteria and methods for evaluating clinical improvement, favor Metrazol (1,3). The only study of i.v. medication in nonsenile depression shows little efficacy (three of 18 improved). There is no evidence presented on treatment of fatigue or psychosis in other than senile conditions.

#### DOCUMENTATION:

1. Mead, S., E. E. Mueller, E. P. Mason, T. Kheim, and W. B. Kountz. A study of the effects of oral administration of metrazol in old individuals. *J. Geront.* 8:472-476, 1953.
2. Pacella, B. L., J. Doltolo, and R. R. Cerulli. Subconvulsive metrazol therapy. *J. Nerv. Ment. Dis.* 117: 50-54, 1953.
3. Swenson, W. M., and B. P. Grimes. Oral use of metrazol in senile patients. *Geriatrics* 8:99-101, 1953.

- II. Geroniazol Injection is used in the treatment of senile depression*

**EVALUATION:** Ineffective.

**COMMENTS:** Same as for Indication I.

**DOCUMENTATION:** Same as for Indication I.

*III. Geroniazol Injection is used in the treatment of  
senile psychosis*

EVALUATION: Ineffective.

COMMENTS: Same as for Indication I.

DOCUMENTATION: Same as for Indication I.

*IV. Geroniazol Injection is used in the treatment of  
senile fatigue*

EVALUATION: Ineffective.

COMMENTS: Same as for Indication I.

DOCUMENTATION: Same as for Indication I.

*V. Geroniazol Injection is used in the treatment of  
senile debilitation*

EVALUATION: Ineffective.

COMMENTS: Same as for Indication I.

DOCUMENTATION: Same as for Indication I.

**GENERAL COMMENTS**

There is no rationale for the parenteral use of this preparation.

Approved by

\_\_\_\_\_,  
Chairman,

**PANEL ON DRUGS USED IN ANESTHESIOLOGY**

**INDICATIONS**

*I. Geroniazol is indicated as an analeptic*

EVALUATION: Ineffective.

COMMENTS: The suggested indications are senile confusion, depression, psychosis, fatigue, and debilitation. Geroniazol is claimed to exert its action through respiratory and circulatory stimulation and vasodilation. The beneficial effect of this combination of two drugs, pentylenetetrazol and nicotinic acid, is credited to the respiratory and circulatory stimulant actions of pentylenetetrazol and the peripheral vasodilator action of nicotinic acid.

There is no evidence, direct or indirect, to support either the mechanism of action or the action itself. Consequently, Geroniazol must be judged ineffective as an analeptic. This drug has had no proper clinical evaluation.

DOCUMENTATION: None.

#### GENERAL COMMENTS

The insert gives 12 references to the use of the product. On a separate list are 24 references to the use of pentylenetetrazol, three to the use of nicotinic acid, and two more to the use of Geroniazol.

Of the 41 references, none qualifies as proper drug evaluation. Two papers give more information than the rest.

(1) Lieberman, A. L. et al: Evaluation of intravenous and oral use of metrazol in hospitalized arteriosclerotic psychiatric patients. *Geriatrics* 9:371, 1954.

This is a comparative study of the effect of pentylenetetrazol (not Geroniazol) and a placebo in 41 arteriosclerotic psychiatric patients. The evaluation was by psychologic testing and clinical impression. The authors found improvement by clinical impression in one-third and one-half of the patients in the two treated groups, and in one-fourth of the patients receiving placebo. There was no change by psychologic testing.

(2) Levy, S.: Pharmacological treatment of aged patients in a state mental hospital. *JAMA* 153:1260, 1953.

This is a study of 30 patients, most of them suffering from the chronic brain syndrome. The effect of Geroniazol is compared with that of a placebo in a double-blind study. The results are not presented in sufficient detail to permit evaluation; no statistical analysis is done. The author claims marked improvement in behavior and a better performance on psychologic testing.

The Panel has been unable to find any relevant controlled studies in man of either Geroniazol, pentylenetetrazol, or nicotinic acid.

Approved by

\_\_\_\_\_  
Chairman.

## PANEL ON DRUGS USED IN RESPIRATORY DISTURBANCES

### INDICATIONS

#### *I. Respiratory stimulation*

**EVALUATION:** Ineffective.

**COMMENTS:** This compound acts as a general central nervous system stimulant, and this indirectly results in some respiratory stimulation. In the opinion of the Panel, this effect is too transient (because of rapid inactivation) for pentylene-tetrazol to be an effective respiratory stimulant itself. However, any respiratory stimulation that may occur does so at a cost of increased oxygen consumption and carbon dioxide production.

#### **DOCUMENTATION:**

1. Curran, T.R., and D.K. Phelps. Sustained release pentylenetetrazol-nicotinic acid therapy in senile patients. *Amer. Practit.* 11:617-619, 1960.

2. Esplin, D.W., and B. Zablocka. Central nervous system stimulants; I. Strychnine, picrotoxin, pentylenetetrazol, bemegride, nikethamide, and miscellaneous agents (ethamivan, fluorothyl), pp. 345-353. In L.S. Goodman and A. Gilman, Eds. *The Pharmacological Basis of Therapeutics*. (3rd ed.) New York: The Macmillan Co., 1965.

Approved by

SOL KATZ,  
Chairman.

36 F.R. 3372 (February 23, 1971)

### *Food and Drug Administration*

#### **DRUGS FOR HUMAN USE**

#### **New Drugs on the Market Without Approved New-Drug Applications; Statement of Policy**

The Food and Drug Administration is seriously concerned about the continued introduction into the market of new products without submission and approval through the new-drug procedures of the Federal Food, Drug, and Cosmetic Act. This appears to result from a misunderstanding of the new-drug



requirements or from a deliberate effort to avoid the new drug procedures.

The Commissioner wishes to make it entirely clear that he will require strict adherence to the new-drug requirements. Anyone introducing a new product, or an old product for a new use, or a new combination of old ingredients, or any other product that is or may be a "new drug" under section 201(p) of the Act, and the interpretations provided thereunder by regulations and court decisions, must submit and obtain new-drug approval prior to marketing the preparation. Should a manufacturer or distributor undertake to decide unilaterally that any such product does not require new-drug approval, he must recognize that he risks criminal and civil regulatory action, as well as a probable recall of the product from the market. The burden will be upon such a person to establish that there was, and that he acted upon, a body of published medical data, available to experts in the medical profession generally, from which such experts could fairly and responsibly reach a conclusion that the safety and effectiveness of the particular preparation for the conditions for which it is intended have been so well documented that the composition of the product is such that it would be generally recognized as both safe and effective for the conditions for which the drug is prescribed, recommended, or suggested in its labeling.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 505, 701(a), 52 Stat. 1041-42, as amended, 1052-53, as amended, 1055; 21 U.S.C. 321(p), 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), it is proposed that the following new section be added to Subpart A of Part 130:

**§ 130. - - - - NEW DRUGS ON THE MARKET WITHOUT APPROVED  
NEW-DRUG APPLICATIONS.**

(a) The Food and Drug Administration published a statement of policy on May 28, 1968 (33 F.R. 7758), § 130.39 (21 CFR 130.39), revoking all opinions theretofore given that an article was "not a new drug" or was "no longer a new drug." That policy states that undisclosed or unreported side effects, as well as the emergence of new knowledge presenting questions with respect to the safety or effectiveness of a drug, may result in its being a "new drug" even though it may previously have been considered "not a new drug." The Food and Drug



Administration is publishing its requirements for continued marketing of these and other drugs through the process of implementing the conclusions of the NAS/NRC Drug Efficacy Study on labeling claims made for drugs marketed under the new-drug and antibiotic drug procedures between 1938 and 1962.

(b) In implementing the conclusions of the Drug Efficacy Study and identifying all marketed drugs affected by this review, it is apparent that large numbers of drugs have been, and continue to be, introduced to the market without clearance through the new-drug procedures and without the manufacturer or distributor having reached an understanding with the Food and Drug Administration that new-drug approval is not required. These include products with new formulations, new manufacturers, new manufacturing procedures, and new or revised claims. Most, if not all of these products are new drugs and should have been cleared through the new-drug procedures prior to marketing.

(c) The marketing of a new drug based on a conclusion by the manufacturer or distributor that the drug does not fall within the statutory definition of a "new drug" because its composition is such that the particular drug would be generally recognized among appropriately qualified experts as safe and effective for its labeled indications is a risk that may ultimately result in injury to patients or ineffective treatment, and may subject the manufacturer or distributor to civil and criminal liability and to product recall. The manufacturer or distributor must be prepared to support any such unilateral decision by the medical documentation upon which it can be concluded by qualified experts that the safety and effectiveness of the drug for the conditions for which it is intended are so well established that the product would be generally recognized as safe and effective for the conditions for which it is labeled.

(d) The determination whether a drug is generally recognized as safe and effective for any condition is complex and not an absolute or one-time determination. The judgment requires consideration of the composition of the drug in terms of its reproducibility and reliability, as well as the indications for its use. Since product reproducibility and reliability require adherence to the conditions of current good manufacturing practice, including when applicable assurance of bioavailability, there are few if any times that an expert judgment can be

reached without full knowledge of factors that affect product composition. This consideration alone means that new-drug approval will be required in essentially all cases. The judgment is affected by new knowledge pertaining to adverse effects from the drug and by new considerations applicable to the treatment of the condition or disease involved. Full information necessary to sustain an expert judgment as to safety and effectiveness of a drug may not be available to the manufacturer or distributor or to the experts upon whom he relies. The Food and Drug Administration believes that before a manufacturer or distributor introduces a product to the market, whether or not the same or a similar product is already marketed by another firm, a request for review and comment on the proposal should be submitted. Information submitted should include a complete statement of the composition (active and inactive ingredients, and assurance of product reliability), the labeling, and an adequate summary of the medical documentation on which the manufacturer or distributor and his expert advisors have reached a decision that the composition of the drug is such that it is generally recognized as safe and effective for the conditions for which it is to be prescribed, recommended, or suggested in its labeling.

(e) Manufacturers and distributors of drugs on the market which have not been cleared through the new-drug procedures should undertake an immediate study of all such drugs, their composition, their labeling, and the available evidence of safety and effectiveness upon the basis of which the products have been marketed. Appropriate steps should be taken to remove from the market drugs not supported by adequate evidence of safety and effectiveness and to bring all drugs that are to remain on the market into full compliance, including compliance with the new-drug provisions. The Food and Drug Administration is prepared to give advice on all drugs upon written inquiry setting forth the complete composition, the labeling, and an adequate summary of the medical documentation supporting the safety and effectiveness of the product.

Interested persons may, within 30 days after publication hereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-62, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding this proposal. Com-

ments may be accompanied by a memorandum or brief in support thereof.

Dated: February 17, 1971.

SAM D. FINE,  
*Associate Commissioner for Compliance.*

[FR Doc.71-2414 Filed 2-22-71 ;8:46 am]

[Original filed, February 10, 1971, Miller C. Foster, Jr., clerk]

In the District Court of the United States for the District of  
South Carolina, Greenville Division

Civil Action No. 70-1001

[Caption omitted]

ORDER

This is a civil action for declaratory and injunctive relief brought by twenty-four pharmaceutical companies aggrieved by the action of the Food and Drug Administration (hereinafter F.D.A.) respecting drugs containing pentylenetetrazol. The events leading to the commencement of this action may be summarized as follows: In August 1969 the F.D.A. announced in the FEDERAL REGISTER its intention to initiate proceedings to withdraw approval of new drug applications for two drugs containing pentylenetetrazol and nicotinic acid. (34 F.R. 13673) The drugs covered by those applications differed from those manufactured by the plaintiffs herein in that the product covered by one application was injected intravenously and the other application contained a third active ingredient, reserpine. The published notice invited the submission of data on the efficacy of the products by any interested person who might be adversely affected by the removal from the market of the drugs covered by the new drug applications. The notice further stated:

Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

None of the plaintiffs herein responded to the notice and in May 1970, a second notice was published stating that substantial evidence of the effectiveness of the drugs covered by the new drug applications had not been provided and that the approval of the application would be withdrawn. Notice was also given that any affected person desirous of a hearing on the question should so elect within 30 days (35 F.R. 7749). That notice contained language concerning the effect on drugs other than those covered by the applications to be withdrawn substantially identical to the language of the August notice set out above.

In September 1970 the F.D.A. published its order withdrawing approval of the two new drug applications mentioned above and directing the recall of outstanding stocks of the drugs. 35 F.R. 14412.

Pursuant to its revocation of the two new drug applications, the F.D.A. took steps to effect the removal from the market of drugs containing pentylenetetrazol manufactured by various of the plaintiffs. By their complaint in this action the plaintiffs seek declaratory judgment determining the validity and enforceability of the order of the Secretary as it concerns their drugs and injunctive relief *pendente lite*. The defendants moves that the action be dismissed for want of jurisdiction and failure to state a claim for which relief can be granted.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, *et seq.*) effective in 1938, gave preclearance authority to the Food and Drug Administration to regulate the distribution of new drugs by a system of new-drug applications which had to be obtained before distribution of the drug in interstate channels was allowed. The early definition of new drugs, however, gave the Agency power to regulate these drugs and approve them on the basis of safety alone. The drug companies were not required to support their claims of effectiveness for the drug with appropriate medical data. Effective on October 10, 1962, the Act was amended to close this important gap in the regulatory power of the Agency. Under the provisions of the Act as amended, a drug not only must be proved safe, but also must be shown by "substantial evidence," to be effective for the indication and uses described in its labeling. The amendments also define "substantial evidence" as consisting of "... adequate and well-controlled investigations, including clinical investigations, by experts . . ." sufficient to demonstrate that the drug

works as claimed. [21 U.S.C. 355(d)]. The burden of producing evidence of effectiveness to support continued marketing of drugs which have already been cleared on the grounds of safety, is placed squarely on the drug manufacturers and distributors. [21 U.S.C. 355(b)]. The Act as amended also gives the Secretary power to revoke approved new drug applications for several reasons among which is failure to submit substantial evidence of the effectiveness of the drug [21 U.S.C. 355(e)3]. It was pursuant to this authority that the Secretary issued the order by which the plaintiffs herein are aggrieved.

The Act grants the Secretary primary jurisdiction to make determinations regarding new drug applications and provides direct appeal from his orders to the circuit courts.<sup>1</sup>

The plaintiffs do not contend that this court has jurisdiction to consider the propriety of the Secretary's revocation of the

<sup>1</sup> 21 U.S.C. § 355(h). An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 23, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the Court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

two new drug applications. Rather they argue either that their drugs are not new drugs within the meaning of the Act or are within the grandfather clause;<sup>2</sup> and are therefore not subject to the Secretary's regulation of new drugs. The plaintiffs contend that seizure, injunction, or criminal prosecution by the F.D.A. pursuant to 21 U.S.C. §§ 332-34 is imminent.<sup>3</sup> They urge that, rather than proceeding at their peril, they are entitled to declaratory relief adjudicating the merits of their respective contentions concerning the status of their drugs.<sup>4</sup> They

<sup>2</sup> 21 U.S.C. § 321 (p). The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigation, been used to a material extent or for a material time under such conditions.

<sup>3</sup> The plaintiff Bentex Pharmaceutical Company received the following letter from F.D.A.:

Nov. 4, 1970.

"This letter is written in reference to your products Benizol Tablets & Elizir, Benizol A-D Tablets, & Benizol Plus capsules & Elizir containing Pentylene-tetrazol for human use.

"On September 12, 1970, an announcement published in the *Federal Register* setting forth the conclusion of the Food and Drug Administration that there is a lack of substantial evidence that drugs similar to yours are effective for the uses prescribed, recommended, or suggested in their labeling.

"Accordingly, the Commissioner of the Food and Drug Administration has withdrawn approval of the applicable new drug applications for such drugs.

"The withdrawal of all previously approved new drug applications causes any similar drug to be a new drug for which an approved new drug application is not in effect. Because these are no longer regarded as legal products, any such drug on the market is subject to regulatory proceedings under the applicable provisions of the Federal Food, Drug, and Cosmetic Act.

"We request your reply within 15 days after receipt of this letter stating your intentions with respect to removal of all outstanding stocks of your product to the retail level."

<sup>4</sup> It appears that for a time drugs of the type in question were regarded as old drugs by the F.D.A. The record contains a letter dated Dec. 15, 1958 which reads in pertinent part as follows: "As to your inquiry



argue persuasibly that they are entitled to a day in court on that question prior to the seizure of their products and possible criminal prosecution.

The plaintiffs urge that they can only have that day in this court. The court does not agree. The Act gives the F.D.A. authority to proceed by seizure action, criminal prosecution, or injunction, [21 U.S.C. 332-334] to clear the channels of interstate commerce of drugs which have improperly avoided the new drug procedures. This grant of authority to approve or withhold approval of new drug application, or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment. The determination that drug is a new drug is essential to any F.D.A. action regulating it by means of new drug applications. Therefore, the F.D.A. must have jurisdiction to make that determination.<sup>6</sup>

The defendant, on the other hand, urges that this court does not have jurisdiction to consider and determine the status of the drugs in question, that the F.D.A. has primary and exclusive jurisdiction with appeal to the circuit court. That contention is likewise without merit. There is no doubt that the F.D.A. does have primary jurisdiction to make determinations concerning the safety and effectiveness of new drugs. Its expertise is necessary for consideration of the complex and technical nature of the factual issues to be evaluated.<sup>6</sup> That question is not, however, in dispute in this instance. The contention urged by the plaintiffs that its drugs are old or grandfathered, must turn upon the court's conclusion as to whether among qualified experts there was general recognition of the

concerning the new drug status of a timed disintegration tablet containing Pentylene-tetrazol 300 mg., Nicotinic Acid 150 mg. In our opinion this article is not a new drug as defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act when distributed as a prescription preparation under the labeling which you have submitted." Statements such as the above were, however, revoked by the Secretary [21 C.F.R. 130.39].

<sup>6</sup>Hymson, Wescott and Dunning, Inc. v. Finch, C.A. 2112, D. Md., decided September 16, 1970, on facts represented to the court to be similar to the present case held that the F.D.A. could consider and decide questions determining the status of a drug and that review of that determination would be available pursuant to 21 U.S.C. 355(h) set out at n. 1, supra.

<sup>7</sup>See e.g. *Far East Conference v. United States*, 342 U.S. 570 (1952); *Tyler Pharmacal Dist. v. H.E.W.*, 408 F. 2d 95 (7th Cir. 1969); *Lemmon Pharmacal Co. v. Richardson*, C.A. 68-921, E.D. Pa. 1970.

safety and efficacy of the drug. [*United States v. "Quick-O-Ver"*, 274 F. Supp. 443 (1967)]. Counsel for the defendants acknowledged that the fact that the drugs were old or grandfathered would be a defense to be raised and considered in the district court when and if the F.D.A. sought sanctions against the plaintiff manufacturers.

The remaining question regarding the jurisdiction of this court is whether the action for declaratory judgment may be maintained in its present posture. The opinions of the Supreme Court in *Abbott Laboratories v. Gardner*, 387 U.S. 136 (1967) and *Toilet Goods Assn. v. Gardner*, 387 U.S. 158 (1967) convince this court that the present matter is properly before it. As pointed out in those cases, there is nothing in the Food, Drug and Cosmetic Act [21 U.S.C. § 301, *et seq.*] which bars a pre-enforcement suit under the Administrative Procedure Act [5 U.S.C. §§ 701-704] and the Declaratory Judgment Act [28 U.S.C. § 2201]. The language in the Secretary announcement of May 20, 1970, of which the plaintiffs complaint and pursuant to which the Secretary apparently intends to proceed against them, is apparently final within the meaning of 5 U.S.C. § 704. (*Abbott*, *supra*, at 692) The letter of the F.D.A. set out above in note 4, indicates that action against the plaintiffs is imminent. The affidavits of the plaintiffs show that the threatened action will result in substantial injury to them. Therefore, this matter is properly before this court and the defendant's motion to dismiss is denied.

The court indicated above that the F.D.A. has jurisdiction to determine whether the drugs in question are new drugs. The court is of the opinion that, even though that determination can be made in this forum, the nature of the proof relevant to that issue makes the F.D.A. the more able arbiter of the question. However, if such determination is to be binding upon the plaintiffs in this action and the industry in general, parties interested in the status of drug combinations must be given an opportunity to be heard. They must be provided a day in court on the issue, during which a record can be made, on which record appeal to the circuit court can be had. That procedure would produce a resolution to the question which would bind the industry and remove the issue from subsequent, and perhaps numerous, enforcement actions. These plaintiffs quite properly point out that they have as yet had no opportunity to be heard on the question of whether their products are new drugs within the meaning of



the Act; and it does not appear that such hearing could have been required of the F.D.A. by the plaintiffs. Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background. The court's opinion in this regard has influenced it considerably in its consideration of appropriate temporary relief.

The area of regulation of drugs is one which the court enters with great reluctance. However, the affidavits of the plaintiffs convince the court that they may suffer substantial business losses, perhaps unnecessarily, if the court refuses to grant temporary relief. As the court understands the record before it and the argument of counsel, there is no contention that the use of the plaintiff's drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs. The court's order, being based upon this hypothesis, will be vacated upon a sufficient contrary showing by the defendant and, upon request by the defendant, the court will arrange to hear its proof in that regard.

The situation revealed by the record to date convinces the court that the status quo must be preserved until such time as the plaintiffs have an opportunity to be heard on the merits of their contention. Therefore, the court will enjoin the defendants from instituting actions against the plaintiffs on account of such of their products as are presently marketed, as contain combinations of pentylenetetrazol and nicotinic acid, are distributed by prescription, and are for treatment of symptoms of senility in geriatric patients; and the defendants are hereby enjoined from instituting any action against the plaintiffs herein for the cause stated above until such time as there has been a determination that the products in question are new drugs. Recognizing the desirability of the F.D.A.'s making such determination, after a hearing of the matter, this court will defer further proceedings herein upon a showing by the defendants that such hearing will be held. It will dissolve the injunction herein ordered, and dismiss the presentation upon resolution of the question by the F.D.A. after a hearing.<sup>7</sup> Should the F.D.A.

<sup>7</sup> A court has considerable discretion in proceeding in actions for declaratory judgment, and may dismiss such actions if they are pending in litigation elsewhere. *Abbott Laboratories v. Gardner*, 387 U.S. 136, 155 (1952).

decline to hold such hearing, the matter must proceed to determination in this court.

*And It is so ordered.*

Robert W. Hemphill  
ROBERT W. HEMPHILL,  
*United States District Judge.*

Columbia, South Carolina. FEBRUARY 10, 1971.

[A true copy.

Teste:

MILLER C. FOSTER, Jr.  
Clerk, by: *Deputy Clerk.*]

In the United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP.,  
MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL  
COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMA-  
CEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON  
PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC.,  
SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN  
PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL  
ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHAR-  
MACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO  
PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES,  
INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMA-  
CEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E.  
BOODY & Co., APPELLANTS

v.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE AND CHARLES C. ED-  
WARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRA-  
TION, APPELLEES

Appeal From the United States District Court for the District  
of South Carolina, at Greenville. Robert W. Hemphill, Dis-  
trict Judge

Argued December 8, 1971—Decided May 23, 1972

Before WINTER, RUSSELL, and FIELD, Circuit Judges

George F. Townes (Sol E. Abrams on brief) for Appellants,  
and Charles R. McConachie, Attorney, Department of Justice

(Will Wilson, Assistant Attorney General, John L. Murphy, Chief, Administrative Regulations Section, William W. Goodrich, Assistant General Counsel, Food, Drugs, and Environmental Health Division, Robert N. Anderson, Attorney, United States Department of Health, Education, and Welfare, and Howard S. Epstein, Attorney, Department of Justice, on brief) for Appellees.

**RUSSELL, Circuit Judge:** This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.<sup>1</sup> 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education, and Welfare.<sup>2</sup> The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof \* \* \*."<sup>3</sup> From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.<sup>4</sup> Drugs, which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination.

<sup>1</sup>There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316-27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

<sup>2</sup>Section 355(a), 21 U.S.C.: The actual approval of a "new drug" under the act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

<sup>3</sup>Section 321 (p) (1), 21 U.S.C.: See also, *United States v. Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445, n. 2: "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

<sup>4</sup>Section 355(h), 21 U.S.C.

The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice".<sup>5</sup> Accordingly, the responsibility for determining whether its product is a "new drug", requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.<sup>6</sup> If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug", it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;<sup>7</sup> its sale may be enjoined in an action begun by the Government;<sup>8</sup> in addition, the manufacturer may be subjected to criminal action.<sup>9</sup> All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug", with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court*.

Under the 1938 Act, a new drug was one "not generally recognized by experts \* \* \* as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug", the Amendments defined a drug as "new" if it were not generally recognized as both safe and effective. Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.<sup>10</sup> They pro-

<sup>5</sup> 21 C.F.R. 130.39.

<sup>6</sup> Cf. *United States v. Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said: "In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

<sup>7</sup> Section 334, 21 U.S.C.

<sup>8</sup> Section 332, 21 U.S.C.

<sup>9</sup> Section 333, 21 U.S.C.

<sup>10</sup> Section 355(c), 21 U.S.C.

ceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.<sup>11</sup> For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug application, \* \* \*) "on the day immediately preceeding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.<sup>12</sup> In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments."<sup>13</sup>

<sup>11</sup> Section 107(c) (3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

<sup>12</sup> Section 107(c) (4), P.L. 87-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmaceutical Distrib. Inc. v. U.S. Dept. of Health, E. & W.* (7th Cir. 1969) 408 F. 2d 95, 99; It should be noted that Section 321(p) (1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c) (4).

<sup>13</sup> Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971); See, also, *United States v. Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

"Thirdly, in the case of a drug on the market which was never

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States v. Article of Drug Labeled Decholin* (D.C. Mich. 1967) 264 F. Supp. 473, 482-3; *United States v. Lanpar Company* (D.C. Tex. 1968) 293 F. Supp. 147, 153-4.<sup>14</sup> Accordingly, in *United States v. Guardian Chemical Corporation* (2d Cir. 1969) 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments*, 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).<sup>15</sup>

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subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U.S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

<sup>14</sup> See, also, *Pfizer, Inc. v. Richardson* (2d Cir. 1970) 434 F. 2d 536, 548: "A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

<sup>15</sup> See, also, Senate Report #1744, *U.S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in



The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,<sup>16</sup> without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."<sup>17</sup> Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effective-

justifying the Amendments. It is stated: " \* \* \* where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. \* \* \* No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

<sup>16</sup>This was the day "immediately preceding the enactment date" of the Amendments of 1962.

<sup>17</sup>It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated v. Gardner* (D.C.N.Y. 1967) 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U.S. 825, reh. den. 395 U.S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States v. 60 28-Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F. Supp. 207, 215, aff. 325 F. 2d 513.

tiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause", Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.<sup>18</sup> Faced with this threat, the plaintiffs began this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met

<sup>18</sup> The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at pp. 203-207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).



the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs", requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause".

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs", on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause".<sup>19</sup> However—and this is the nub of the controversy between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs", requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause". It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause". It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs",

<sup>19</sup> In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories v. Gardner* (1967) 387 U.S. 136 and the companion case of *Toilet Goods Assn. v. Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated v. Gardner, supra*; *Durovic v. Richardson* (D.C. Ill. 1971) 327 F. Supp. 386; *Lemmon Pharmacal Co. v. Richardson* (D.C. Pa. 1970) 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States v. Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445; and *United States v. Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F. Supp. 107, 112, n. 13, aff. 415 F. 2d 369.

as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator or either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug". There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary.

It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory judgment action.<sup>20</sup> Moreover, when FDA undertook its new responsibilities under 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared*, for safety only, between 1938 and October 10, 1962"<sup>21</sup> (Italics added) and enlisted the services of the National Academy of Sciences-National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the

<sup>20</sup> See, *Hynson, Westcott & Dunning, Inc. v. Richardson* (Civ. No. 2112 D. Md., decided 9/16/70); and *Ciba Corp. v. Richardson* (Civ. No. 1210-70, D.N.J., decided 3/10/71); but cf., *Lemmon Pharmacal, supra*.

<sup>21</sup> See *Pfizer, Inc. v. Richardson* (2d Cir. 1970) 434 F. 2d 536, 539, and 31 F.R. 9426.

approval, or the withdrawal of approval,<sup>22</sup> of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.<sup>23</sup> Those are the procedures prescribed and available to the Government under the Act.<sup>24</sup> The Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".<sup>25</sup> The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.<sup>26</sup> That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel v. Food and Drug Administration, Dept. of H.E.W., supra*, at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and

<sup>22</sup> The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

<sup>23</sup> Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

<sup>24</sup> Cf. *United States v. Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. den. 385 U.S. 899, in which the Secretary is quoted to the effect that, "As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court*, insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure." (Italics added.)

<sup>25</sup> See *Turkey v. Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964) 334 F. 2d 844, 846, cert. denied 379 U.S. 990, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

<sup>26</sup> Section 355(b), 21 U.S.C.

distribution of a new drug" (at pp. 845-6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug".<sup>27</sup>

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, \* \* \* necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as a "new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act.

The criterion for ascertaining whether a product is within statutory definition of "new drug" under the Act is not safety and effectiveness *per se*, which as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the evidence that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions pre-

<sup>27</sup> Cf., *Abbott Laboratories v. Gardner* (1967) 387 U.S. 136, at p. 140.

scribed, recommended or suggested in the labeling thereof.”<sup>28</sup> That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States v. Articles of Drug Labeled “Quick-O-Ver”*, *supra*; *United States v. 41 Cases, More or Less* (5th Cir. 1970) 420 F. 2d 1126, 1128; *United States v. Article of Drug, etc.*, *supra*, at p. 392; *United States v. Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F. 2d 734, 742; *United States Article Consisting of 36 Boxes, etc.*, *supra*, at p. 113; see, also, *United States v. Article of Drug, etc.* (D.C. Md. 1971) 331 F. Supp. 912, 915-7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co. v. Richardson*, *supra*.<sup>29</sup> It is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs’ drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs’ products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.<sup>30</sup> Upon remand, the issue

<sup>28</sup> *United States v. Articles of Drug Labeled “Quick-O-ver”*, *supra*, at pp. 445-6.

See, also: *AMP, Incorporated v. Gardner*, *supra*, at p. 831: “But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products’ safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education, and Welfare for a determination as to safety, adequacy of testing, etc.”

*United States v. Article of Drug, etc.* (5th Cir. 1969) 415 F. 2d 390, 392: “Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue.”

Cf., *United States v. Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F. 2d 1364, 1365.

<sup>29</sup> In discussing this case, the commentator in 60 *Georgetown Law Journal*, p. 199, note 87, says: “In *Lemmon Pharmacal*, the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it.”

<sup>30</sup> See *United States v. Article Consisting of 36 Boxes etc.*, *supra*, at p. 113.

can be considered by the Court in the light of the record that may be made by the parties.

*Remanded with directions.*

[Filed, May 23, 1972, Samuel W. Phillips, clerk.]

In the United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL  
CORP., ET AL., APPELLANTS

v.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE AND CHARLES C.  
EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMIN-  
ISTRATION, APPELLEES

Appeal from the United States District Court for the District  
of South Carolina.

*Judgment*

This cause came on to be heard on the record from the United States District Court for the District of South Carolina, and was argued by counsel.

On consideration whereof, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this cause, be, and the same is hereby, reversed. The case is remanded to the United States District Court for the District of South Carolina, at Greenville, with directions consistent with the opinion of this Court filed herewith.

SAMUEL W. PHILLIPS,  
Clerk.

Supreme Court of the United States

No. 72-555

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION,  
AND WELFARE, ET AL., PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

Order allowing certiorari. Filed January 8, 1973.

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72-394, 72-414, 72-528 and 72-666, and a total of three hours is allotted for oral argument.



## United States Court of Appeals for the Fourth Circuit

Civil No. 71-1596

USV PHARMACEUTICAL CORPORATION, APPELLANT

v.

ELLIOT L. RICHARDSON, ET AL., APPELLEES

## RELEVANT DOCKET ENTRIES

## Date

- 6/29/71 Record on appeal in three volumes (Volumes I, II, and III) filed and appeal docketed.
- 6/29/71 Exhibits in one volume (Volume IV) received from the Clerk of the District Court at Alexandria, Virginia.
- 6/29/71 Deposition of Theodore H. Spaet in one volume (Volume V) received from the Clerk of the District Court at Alexandria, Virginia.
- 6/29/71 Transcript of proceedings of December 1, 1969 in one volume (Volume VI) filed.
- 6/29/71 Transcript of proceedings of October 19, and 20, 1970 in one volume (Volume VII) filed.
- 6/29/71 Transcript of proceedings of October 23, 1970 in one volume (Volume VIII) filed.
- 6/29/71 Transcript of proceedings of October 26, 1970 in one volume (Volume IX) filed.
- 6/29/71 Transcript of proceedings of May 4, 1971 in one volume (Volume X) filed.
- 7/ 6/71 Appearance for the appellee filed and entered.
- 7/ 6/71 Appearance for the appellants filed and entered.
- 7/14/71 Appellant's motion for extension of time to file brief and appendix to September 10, 1971, filed. Motion granted.
- 7/14/71 Appearance for the appellants filed and entered.
- 8/ 9/71 Appellant's Statement of Issues and Designation of Contents of Record to be included in appendix, filed.
- 9/10/71 Motion for extension of time of the appellants to September 20, 1971, filed. Motion granted.
- 9/27/71 Brief for appellants filed. 25 copies.
- 9/27/71 Joint appendix filed. 10 copies.
- 10/ 7/71 Appellee's motion for extension of time to file brief filed. Motion denied.
- 10/12/71 Order extending the time to file appellee's brief to November 22, 1971, filed.
- 11/16/71 Notice of oral argument mailed to Moncure, Hoffman, Hutt, and Epstein.
- 11/24/71 Brief and appendix for appellees filed. 25 copies.
- 12/ 6/71 Reply brief for appellants filed. 25 copies.
- 12/ 8/71 Cause argued before Winter, Russell, Field, Circuit Judges, and Submitted.



- 12/17/71 Above record on appeal with tape mailed to Judge Russell.
- 5/12/72 Record on appeal in nine volumes received from Judge Russell.
- 5/24/72 Opinion filed.
- 5/24/72 Opinion and Clerk's Memorandum mailed to counsel of record (Mailed to Epstein, Hoffman, and Moncure.) Copy of opinion mailed to the Clerk of the district court at Alexandria, Virginia.
- 5/24/72 Judgment of the district court reversed. Judgment filed.
- 6/ 1/72 Appellant's verified bill of costs, filed.
- 6/ 9/72 Motion for leave to file petition for rehearing out of time to June 9, 1972, filed. Motion granted.
- 6/ 9/72 Petition for rehearing, filed.
- 7/ 5/72 Order denying appellee's petition for rehearing and suggestion for rehearing en banc, filed.
- 7/13/72 Certified copy of the judgment and printed copy of the opinion transmitted to the Clerk of the District Court at Alexandria, Virginia.
- 7/13/72 Record on appeal in three volumes (Vols. I, II and III), exhibits in one volume (Vol. IV), deposition of Theodore H. Spaet in one volume (Vol. V), transcript of proceedings of December 1, 1969 in one volume (Vol. VI), transcript of proceedings of October 19 and 20, 1970 in one volume (Vol. VII), transcript of proceedings of October 23, 1970 in one volume (Vol. VIII), transcript of proceedings of October 26, 1970 in one volume (Vol. IX and transcript of proceedings of May 4, 1971 in one volume (Vol. X) returned to the Clerk of the District Court at Alexandria, Virginia.
- 11/ 3/72 Notice evidencing the filing petition for writ of certiorari in the Supreme Court October 30, 1972 filed. (No. 72-686).
- 1/12/73 Certified copy of order of the Supreme Court granting certiorari January 8, 1973 filed.
- 7/13/72 Record on appeal in three volumes (Vols. I, II and III), exhibits in one volume (Vol. IV), deposition of Theodore H. Spaet in one volume (Vol. V), transcript of proceedings of December 1, 1969 in one volume (Vol. VI), transcript of proceedings of October 19th and 20th, 1970 in one volume (Vol. VII), transcript of proceedings of October 23, 1970 in one volume (Vol. VIII), transcript of proceedings of October 26, 1970 in one volume (Vol. IX and transcript of proceedings of May 4, 1971 in one volume (Vol. X) received from the Clerk of the District Court at Alexandria, Virginia.
- 2/ 2/73 Certified record in ten volumes and exhibits in one envelope transmitted to the Clerk of the Supreme Court.

In the United States District Court for the Eastern District  
of Virginia

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, 800 SECOND AVENUE,  
NEW YORK, NEW YORK 10017, PLAINTIFF

v.

WILBUR J. COHEN, SECRETARY OF HEALTH, EDUCATION AND  
WELFARE, DEPARTMENT OF HEALTH, EDUCATION & WELFARE,  
WASHINGTON, D.C. 20201, AND HERBERT L. LEY, JR., COM-  
MISSIONER OF FOOD AND DRUGS, FOOD & DRUG ADMINISTRA-  
TION, 2221 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VIR-  
GINIA, DEFENDANTS

*Complaint for Declaratory Judgment*

Plaintiff, by its attorneys, brings this civil action and com-  
plains and alleges as follows:

JURISDICTION AND VENUE

1. This action arises under the Federal Food, Drug & Cos-  
metic Act (hereafter "the Act") 52 Stat. 1040 (1938), as  
amended, 21 U.S.C. § 301 *et seq.*, and the Drug Amendments  
Act of 1962 (hereinafter "1962 Amendments") 76 Stat. 789  
(1962). Plaintiff seeks a declaratory judgment that certain of  
its drug products are not "new drugs" within the meaning of  
the Act, and that the 1962 Amendments do not apply to those  
products. There exists between the parties an actual controversy  
on this issue, justiciable in nature, as to which plaintiff requires  
a declaration of its rights by this Court. The jurisdiction of this  
Court is conferred by 28 U.S.C. §§ 1337 and 2201.

2. Defendant Herbert L. Ley, Jr., resides in the Eastern Dis-  
trict of Virginia.

## PARTIES

3. Plaintiff is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business in the State of New York. It manufactures and sells drugs in interstate commerce.

4. Defendant Wilbur J. Cohen is the Secretary of Health, Education and Welfare and is charged by law with the administration of the Act. Defendant Cohen and his predecessors in office will hereafter be referred to as "the Secretary."

5. Defendant Herbert L. Ley, Jr., is the Commissioner of Food and Drugs. He is the head of the Food & Drug Administration, a constituent part of the Department of Health, Education and Welfare. He has been delegated the authority of the Secretary to administer the Act. Defendant Ley and his predecessors in office will hereafter be referred to as "the Commissioner."

## NATURE OF THE CONTROVERSY

6. Plaintiff has from time to time manufactured and sold a variety of products containing citrus bioflavonoid compound (hereafter "bioflavonoids"). These products are the subject-matter of this controversy. Plaintiff presently manufactures and sells the C.V.P. line of products (C.V.P. Capsules, C.V.P. Syrup, C.V.P. With Vitamin K Tablets, C.V.P. With Vitamin K Syrup, Duo-C.V.P. Capsules, and Duo-C.V.P. With Vitamin K Tablets). The conditions of use now represented in the labeling of the C.V.P. products are, in substance, the prevention and treatment of abnormal capillary permeability and fragility, and resultant bleeding when they occur in conditions such as gingival bleeding, habitual abortion, threatened abortion, and nonthrombocytopenic purpura. Prior to 1968, plaintiff also manufactured and sold a bioflavonoid product called Bivam; prior to February 1965, a bioflavonoid product called Prednis-C.V.P.; and prior to May 1961, a bioflavonoid product called Prednyl. Bivam, Prednyl and Prednis-C.V.P. are not now manufactured or sold by plaintiff. They contained the same citrus bioflavonoid compound contained in the C.V.P. line of products.

7. Section 505(a) of the Act (21 U.S.C. § 355(a)) provides that

"no person shall introduce or deliver into interstate commerce any new drug, unless approval of a [new drug] application \* \* \* is effective with respect to such drug."

Until October 10, 1962, the term "new drug" was defined by Section 201(p) of the Act (21 U.S.C. § 321(p)) to mean

"any drug the composition of which is such that such drug is *not generally recognized*, among experts qualified by scientific training and experience to evaluate the safety of drugs, *as safe* for use under the conditions prescribed, recommended, or suggested in the labeling thereof, \* \* \* [or] which has not \* \* \* been [commercially] used to a material extent or for a material time under such conditions" (emphasis added).

The 1962 Amendments (76 Stat. 796), which became effective October 10, 1962, added the criterion of efficacy to the section 201(p) definition, so as to redefine the term "new drug" to mean

"any drug the composition of which is such that such drug is *not generally recognized*, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, *as safe and effective* for use under the conditions prescribed, recommended or suggested in the labeling thereof, \* \* \* [or] which has not \* \* \* been [commercially] used to a material extent or for a material time under such conditions" (emphasis added).

"Grandfather" protection was provided, however, for certain drugs marketed prior to the effective date of the amendments. Section 107(c)(4) of the 1962 Amendments (76 Stat. 789) provides that the new efficacy criterion does not apply

"in the case of any drug which, on \* \* \* [October 9, 1962] (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the \* \* \* [Federal Food, Drug and Cosmetic] Act as then in force, and (C) was not covered by an effective [new drug] application \* \* \* when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

The controversy between plaintiff and defendants is whether plaintiff's bioflavonoid products are entitled to the grandfather protection conferred by Section 107(c)(4).

8. On April 22, 1955, plaintiff filed a new drug application for C.V.P. Capsules, C.V.P. Syrup, and C.V.P. With Vitamin K Syrup. This NDA was designated as NDA 9965, and became effective November 8, 1955. A supplement to NDA 9965 for C.V.P. with Vitamin K Tablets became effective January 19, 1956. A supplement to NDA 9965 for Duo-C.V.P. Capsules became effective May 14, 1956. A new drug application for Prednyl was filed April 3, 1958, designated as NDA 11474, and became effective August 26, 1958. A new drug application for Prednis-C.V.P. was filed April 3, 1958, designated as NDA 11475, and became effective about the same time as NDA 11474. No new drug application or supplement for Duo-C.V.P. With Vitamin K Capsules or for Bivam Tablets was ever filed by plaintiff.

9. On or before October 9, 1962, each of plaintiff's bioflavonoid products was "generally recognized \* \* \* as safe" within the meaning of section 201(p) of the Act; that is, was generally recognized among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended or suggested in the labeling thereof, and had been used to a material extent and for a material time under such conditions otherwise than in investigations to determine its safety for use under such conditions. This was conceded by FDA in correspondence with plaintiff:

(a) On December 12, 1956, believing that its bioflavonoid product Bivam Tablets was "generally recognized \* \* \* as safe," plaintiff wrote a letter to the Food & Drug Administration requesting confirmation that Bivam Tablets was not a new drug. The Food & Drug Administration replied on January 3, 1957, stating that "we do not regard preparations of this composition as new drugs \* \* \*."

(b) On February 28, 1961, believing them to be "generally recognized \* \* \* as safe," plaintiff wrote a letter to the Food & Drug Administration asking whether the products on which, *inter alia*, NDA 9965, NDA 11474, and NDA 11475 had been filed, were "still considered to be 'new drugs'." The Food & Drug Administration replied on April 19, 1961, stating that Prednyl (NDA 11474) and Prednis-C.V.P. (NDA 11475) "are not new drugs when distributed under the labeling provided for in the respective effective new drug applications." In its letter the Food & Drug Administration declined to answer plaintiff's ques-

tion with respect to, *inter alia*, the C.V.P. products (NDA 9965), although the bioflavonoid ingredient therein is the same as in Prednyl and Prednis-C.V.P., and suggested that plaintiff "furnish some information on marketing experience" as well as copies of "labels and labeling." On May 16, 1961, plaintiff responded, enclosing labels and labeling for C.V.P. Capsules, C.V.P. Syrup, C.V.P. With Vitamin K Tablets, C.V.P. With Vitamin K Syrup, Duo-C.V.P. Capsules, and Duo-C.V.P. With Vitamin K Capsules, and stating "it is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective." The Food and Drug Administration did not reply to plaintiff's letter.

10. On May 28, 1968, the Commissioner published in the Federal Register a "Statement of Policy" stating that "all opinions previously given by the Food & Drug Administration to the effect that an article is 'not a new drug' or is 'no longer a new drug' are hereby revoked." The purpose of this "Statement of Policy" was to remove an impediment to later contentions that drugs for which new drug applications had become effective on or before October 9, 1962, were, although generally recognized as safe on that date, subject to section 201(p) as amended by the 1962 Amendments.

11. Section 505(e) of the Act, as amended by the 1962 Amendments, authorizes the Secretary to withdraw approval of a new drug application if he finds

"on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; \* \* \* " (emphasis added).

The May 28, 1968, "Statement of Policy" revoking all previous "not-new" opinions recited that the revocation of previous opinions was "of special importance by reason of proposed actions to withdraw approval of new-drug applications for lack of substantial evidence of effectiveness \* \* \* for example, see the notice published in the Federal Register of January 23, 1968 (33 F.R. 818)."

12. The January 23, 1968, notice stated that "the Food & Drug Administration \* \* \* has concluded \* \* \* that there

is no evidence that \* \* \* bioflavonoids are effective for use in man for any condition"; that the Commissioner "intends to publish a notice of opportunity for a hearing on a proposal to withdraw approval of all new-drug applications for drugs containing \* \* \* bioflavonoids" on the ground, added to the Act in 1962 as alleged above, of no substantial evidence of efficacy; and inviting "all holders of new-drug applications" for bioflavonoid products to a meeting for discussion of procedural matters and for the identification and resolution of "problems that may be anticipated as a result of the actions to be taken." The Commissioner further stated in this Federal Register notice that "promulgation of an order withdrawing approval of \* \* \* new-drug applications [for bioflavonoid products] will classify drugs containing any of these components as new drugs for which an approved new-drug application is not in effect" and that "any such drugs then on the market would be subject to regulatory proceedings."

13. On July 10, 1968, pursuant to the intent stated in his notice of January 23, 1968, the Commissioner published in the Federal Register a notice that he proposed to issue an order under Section 505(e) of the Act, withdrawing approval of, *inter alia*, NDA 9965, NDA 11474, and NDA 11475, on the grounds "that there is a lack of substantial evidence that \* \* \* any bioflavonoid has the effect which the drugs purport to have \* \* \* or that such articles \* \* \* are effective for use in man for any condition." The notice stated that "publication of the proposed order will cause any drug for human use containing any \* \* \* bioflavonoid to be a new drug for which an approved new-drug application is not in effect" and that "any such drug then on the market would be subject to regulatory proceedings." Implicit in this notice is the contention that these products are "new drugs" within the meaning of Section 201(p) of the 1962 Amendments and that the grandfather protection of Section 107(c)(4) does not apply.

14. In fact, each of plaintiff's bioflavonoid products satisfied the conditions of Section 107(c)(4) necessary to qualify for grandfather protection; the amended section 201(p) of the Act therefore does not apply. On October 9, 1962, each of plaintiff's bioflavonoid products for which a new drug application had previously been filed and had become effective was "generally recognized \* \* \* as safe" within the meaning of section 201(p) of the Act; therefore was not a new drug as defined thereby; and



therefore was no longer "covered by an effective new drug application." On October 9, 1962, Duo-C.V.P. With Vitamin K Capsules and Bivam Tablets were "generally recognized \* \* \* as safe" within the meaning of section 201(p) of the Act; therefore were not new drugs as defined thereby; and had never been covered by an effective new drug application. All of plaintiff's bioflavonoid products, with the exception of Prednyl which was discontinued in May 1961, were commercially used or sold in the United States on October 9, 1962.

15. There is an actual controversy, justifiable in character, between plaintiff and defendants as to whether the 1962 Amendments to the definition of the term "new drug" in section 201(p) of the Act apply to plaintiff's bioflavonoid products. Plaintiff has taken the position that the efficacy provisions do not so apply. Defendants have taken the final position that they do; assert that these products are covered by effective NDA's; have instituted, and continue to maintain, administrative proceedings against plaintiff to withdraw approval of the NDA's based upon an alleged lack of substantial evidence of efficacy; and threaten to institute or cause to be instituted other regulatory proceedings against plaintiff on the same basis.

16. The existence of the following controversy requires plaintiff, in order to avoid the threat of criminal prosecution, seizures of its products, and injunction actions, to comply with burdensome administrative regulations, except insofar as compliance therewith may be waived by defendants. Plaintiff will further be required, in order to avoid such threat, to withdraw its bioflavonoid products from the market if approval of its bioflavonoid new-drug applications should be withdrawn by the Commissioner at the conclusion of the pending administrative proceedings. The institution of enforcement actions would in itself severely injure plaintiff in its ability to market its bioflavonoid products. The controversy between plaintiff and defendants cannot be resolved in any pending or future administrative proceeding, but, unless the declaratory judgment prayed herein is granted, can be resolved only in criminal prosecutions, injunction actions or proceedings for seizure and condemnation of the products involved.

Wherefore, plaintiff prays that this Court enter its judgment declaring that plaintiff's bioflavonoid products are not "new drugs" within the meaning of the Federal Food, Drug & Cosmetic Act as amended, and that the efficacy provisions of the



Drug Amendment Act of 1962 do not apply to those products, and plaintiff further prays for such other and further relief as may be just and proper.

ROBERT L. WALD,  
CARLETON A. HARKRADER,  
SELMA M. LEVINE,  
JOEL E. HOFFMAN,  
*Wald, Harkrader & Rockefeller,*  
*1225 Nineteenth Street, N.W.,*  
*Washington, D.C. 20036*  
THOMAS MONCURE,  
*121 South Royal Street,*  
*Alexandria, Virginia 22313.*  
*Attorneys for Plaintiff.*

Dated: AUGUST 6, 1968.

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In the United States District Court For the Eastern District of  
Virginia

[Caption Omitted]

*Answer*

Defendants, by the United States Attorney for this District, for Answer to the Complaint, say:

1. With respect to the allegations in paragraph 1 of the Complaint, Defendants admit that this Court has jurisdiction, but deny that there exists an actual controversy, justiciable in nature; assert that this is not a proper case for the Court's exercise of its discretion under the Declaratory Judgments Act (28 U.S.C. 2201); and assert that the Drug Amendments of 1962, PL. 87-781, do, in fact, apply to Plaintiff's products, which are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act.

2. Defendants deny the allegations of paragraph 2 of the Complaint and assert that the official residence of Herbert L. Ley, Jr., M.D., Commissioner of Food and Drugs, is Washington, D.C.

3. Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 3 of the Complaint.

4. Defendants admit the allegations of paragraph 4 of the Complaint.

5. Defendants admit the allegations of paragraph 5 of the Complaint.

6. Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 6 of the Complaint.

7. Defendants admit the allegations of paragraph 7 of the Complaint, except for the last sentence, which is denied.

8. Defendants admit the allegations of paragraph 8 of the Complaint.

9. With respect to paragraph 9 of the Complaint, Defendants deny the allegations preceding subparts (a) and (b); admit the allegations of subparts (a) and (b), except that Defendants are without knowledge or information sufficient to form a belief as to the allegation in subpart (b) that the bioflavonoid ingredient in the C.V.P. products (NDA 9965) is the same as in Prednyl and Prednis-C.V.P.

10. Defendants admit the allegations of the first sentence and deny the allegations of the second sentence of paragraph 10 of the Complaint

11. Defendants admit the allegations in paragraph 11 of the Complaint.

12. Defendants admit the allegations of paragraph 12 of the Complaint.

13. Defendants admit the allegations of paragraph 13 of the Complaint, except for the last sentence thereof, which is denied.

14. Defendants deny the allegations of paragraph 14 of the Complaint and assert that Plaintiff's products other than Prednyl were commercially used or sold in the United States on October 9, 1962; that the products are not entitled to grandfather protection because the drugs were, on October 9, 1962, new drugs as then defined by Section 201(p) of the Federal Food, Drug, and Cosmetic Act; and/or were covered by effective new drug applications under Section 505 of the Act.

15. Defendants deny the allegations of paragraph 15 of the Complaint, except that Defendants admit taking the position that Plaintiff's products listed in the Notice of Opportunity for Hearing dated July 10, 1968, 33 F.R. 9908, are subject to the efficacy provisions of the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act (Section 201(p)) and that such drugs are covered by effective new drug applications.

16. With respect to the allegations of paragraph 16 of the Complaint, Defendants deny that Plaintiff is threatened by any criminal prosecutions, seizures of its products, or injunction actions, on the basis of the Notice of Opportunity for Hearing dated July 10, 1968, 33 F.R. 9908; and deny that the administrative regulations are burdensome. Defendants assert that Plaintiff has elected to avail itself of the opportunity for hearing on the proposed order to withdraw approval of its new drug applications and assert that, until Plaintiff has fully exhausted its administrative remedies, including review by a United States Court of Appeals upon a timely petition, and by the United States Supreme Court upon certiorari or certification, there is no case or controversy before the Court. Defendants admit that Plaintiff would be required to remove its bioflavonoid drug from the market but only if the final order of the Commissioner, after hearing, withdraws approval of Plaintiff's bioflavonoid new drug applications and if the Commissioner's order is sustained after judicial review under the Act, but assert that the terms of any such order are speculative at this time. Defendants deny all other allegations contained in paragraph 16.

#### *First Affirmative Defense*

Venue is improperly laid before this Court.

#### *Second Affirmative Defense*

There is no controversy, justiciable in nature; Plaintiff is simply party to a hearing on a proposed order to withdraw approval of its new drug applications and has not exhausted its administrative remedies.

#### *Third Affirmative Defense*

The new drug provisions of the Federal Food, Drug, and Cosmetic Act apply to Plaintiff's products. Plaintiff's products are not entitled to grandfather protection under Section 107(c)(4) of the Drug Amendments of 1962, P.L. 87-781, inasmuch as: (1) Prednyl was not commercially used or sold in the United States on October 9, 1962; (2) Plaintiff's products were new drugs as of that date and as then defined by law; and/or (3) Plaintiff's products were covered by effective new drug applications on that date. Plaintiff makes no showing that the third condition of the grandfather section was met: even if Plaintiff's products met the second condition of not being new drugs as of October 9, 1962, they were covered by effective new drug appli-

cations within the meaning of Section 107(c)(4) of the 1962 Amendments. The Notice of Opportunity for Hearing is entirely in accordance with provisions of the Federal Food, Drug, and Cosmetic Act.

#### *Fourth Affirmative Defense*

There is a complete want of equity in the Plaintiff's complaint which should persuade this Court not to exercise discretionary jurisdiction under the Declaratory Judgments Act in that the Plaintiff has been, and seeks to continue, marketing a number of drugs with claims that the drugs will be effective in treating abnormal capillary permeability and fragility (hemorrhagic states), which claims have been and are being made to promote the sale of the drugs despite the Plaintiff's own knowledge derived from a comprehensive review of the medical literature, and despite the report of an independent review conducted by a panel of experts of the National Academy of Sciences-National Council-Drug Effectiveness Study, that there is no substantial evidence that the drugs will have the effectiveness claimed for them and indeed that there is no substantial evidence that the drugs will be effective for any use in man, and it thus would be inequitable for this Court to lend its assistance to the continued marketing of these worthless drugs intended to be sold to the public for medical uses wholly unsupported by substantial medical evidence.

Wherefore, having fully answered the Defendants pray:

1. That the relief requested by the Plaintiff be denied and that the action be dismissed; and
2. That the Defendants be given all such other and further relief as to the Court may seem just and proper.

\_\_\_\_\_,  
*United States Attorney.*

\_\_\_\_\_,  
*Assistant United States Attorney.*

#### *Certificate of Service*

I hereby certify that a copy of the foregoing Motion for Correction of Sentence was mailed, postage pre-paid, to Joel E. Hoffman, Esquire, Wald, Harkrader & Rockefeller, 1225 Nineteenth Street, N.W., Washington, D.C., 20036, this 25th day of October.

JOHN D. SCHMIDTLEIN,  
*Assistant United States Attorney.*

In the United States District Court for the Eastern District  
of Virginia

[Caption Omitted]

*Motion to Dismiss*

Defendants, the Secretary of Health, Education, and Welfare, and the Commissioner of Food and Drugs, by their attorneys, move to dismiss this case for the following reasons and on the following grounds:

1. On October 17, 1970, there was published in the Federal Register an order withdrawing approval of the following new drug applications:

NDA No.	Drug Name	Applicants Name and Address
4-965	C.V.P.; C.V.P. w/Vitamin K; Bivan Tablets: Duo-C.V.P. w/Vitamin K Capsules	U.S. Vitamin Corp., 26 Vark Street, Yonkers, New York, 10701
11-474	Prednyl Tablets.....	Arlington-Funk Labs., Division of U.S. Vita- min Corp., 26 Vark St., Yonkers, N.Y. 10701
11-475	Prednis C.V.P. Capsules.....	Arlington-Funk Labs.

2. The above listed drugs are the subject matter of this action.

3. The Federal Food Drug and Cosmetic Act, 21 U.S.C. 355(h), provides that when an order is entered by the defendants withdrawing approval of any new drug application, appeal is to the United States Court of Appeals for the circuit wherein the applicant resides or has his principal place of business or in the United States Court of Appeals for the District of Columbia Circuit. There is no appeal to any United States District Court.

4. A final order having been entered withdrawing approval of the new drug applications which cover the drugs which are the subject matter of this action, this Court has no jurisdiction and this case must be dismissed for lack of jurisdiction.

\_\_\_\_\_,  
United States Attorney.

\_\_\_\_\_,  
Assistant United States Attorney.

*Certificate of Service*

I hereby certify that on this 19th day of October 1970 I served a copy of the foregoing Motion to Dismiss and Points and Authorities in Support of said Motion by mailing same, postage prepaid to Thomas Moncure, Esquire, 121 South Royal Street, Alexandria, Virginia 22314.

HOWARD S. EPSTEIN,  
*Attorney, Department of Justice.*

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In the United States District Court for the Eastern District  
of Virginia

[Caption Omitted]

*Motion for Clarification of Order and Memorandum Opinion*

Plaintiff USV Pharmaceutical Corp. respectfully requests the Court's guidance in interpreting the order and memorandum opinion filed herein on April 1, 1971. Specifically, we ask the Court to confirm that in its order and opinion the Court has found:

1. That plaintiff's bioflavonoid products here in question are, today, not "new drugs" under the pre-1962 statutory definition of the term, and therefore exempt from the "new drug" provisions of the statute.

2. That on October 9, 1962 plaintiff's bioflavonoids were, and are today, generally recognized by qualified experts as safe for their intended uses, as the word "safe" was then understood.

Respectfully submitted,

THOMAS MONCURE,  
121 South Roy Street,  
Alexandria, Virginia 22314.

SELMA M. LEVINE,  
JOEL E. HOFFMAN,  
Wald, Harkrader, Nicholson & Ross,  
1320 Nineteenth Street, N.W.,  
Washington, D.C. 20036.

APRIL 12, 1971.

I certify that I have caused a copy of the foregoing Motion to be served by hand upon the U.S. Attorney, United States Court House, Alexandria, Virginia, this 12th day of April, 1971.

JOEL E. HOFFMAN.

31 F.R. 13014 (October 6, 1966)

*Food and Drug Administration*

## ANTIBIOTIC DRUGS

## REPORTS OF INFORMATION FOR DRUG EFFECTIVENESS

There was published in the Federal Register of July 9, 1966 (31 F.R. 9426) information pertaining to the agreement by the National Academy of Sciences-National Research Council to assist the Food and Drug Administration in its review of the claims of effectiveness for drugs cleared through the new-drug procedures, pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, from 1938 until October 10, 1962. This agreement also provides for a review of effectiveness of antibiotic drugs certified or exempted from certification under the provisions of section 507 of the act prior to October 10, 1962, as well as to antibiotic drugs cleared through the new-drug procedures but not subject to the certification provisions of section 507 of the act prior to October 10, 1962.

To facilitate this review and to facilitate a determination as to whether any certification or release should be rescinded or whether any regulation issued under section 507 of the act should be amended or repealed, and to give persons described below an opportunity to present for consideration of the reviewing experts the best data available to support the medical claims, this order is entered pursuant to section 507 of the act:

1. Each person engaged in manufacturing, compounding, processing, packing, or labeling any antibiotic drug in dosage form (other than distributor whose labeling is identical, except for such information as distributors' trade names, and addresses, to that under which such antibiotic drug is marketed by its supplier), which antibiotic drug is certified, released, or exempted from certification under the provisions of section 507 of the act on any basis other than approval of a form "5" after October 9, 1962, or an investigational exemption shall report the following in duplicate preferably on forms which have been revised by the National Academy of Sciences—National Research Council and which are available for this purpose from the Food and Drug Administration or any of its offices:

- a. Date originally approved (whether approval is for a form 5, 6, or a new-drug application), new-drug application number,

if any, section of antibiotic regulations (21 CFR) providing specifications therefor, and whether prescription or over-the-counter drug.

- b. Brand name of drug or preparation.
- c. Applicant's (firm's) name and address.
- d. Quantitative formula using established (nonproprietary) name of active ingredients.
- e. Dosage form and route of administration. Where a new-drug application, form 5, or form 6 covers different routes of administration, separate forms should be used.
- f. Current labels and package inserts (attach 10 copies of each to original of form; one copy of each to duplicate).
- g. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure. Approximately 5 to 10 key references, if available (attach 10 copies of the list to original of form and one copy to duplicate).
- h. Unpublished articles or other data pertinent to an evaluation of the claims (one copy only; attach to duplicate).

2. This report shall be made as promptly as possible and no later than 20 days from the date of this publication in the FEDERAL REGISTER, shall be plainly marked on the outside of the envelope or package "Special Antibiotic Report," and shall be addressed to the Director, Bureau of Medicine (or Director, Bureau of Veterinary Medicine, in the case of veterinary drugs), Food and Drug Administration, Washington, D.C. 20204.

3. The submission of this special report may be made without prejudice to any person's contention that he is not required by law to make the report.

4. This order is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507(g), 59 Stat. 463, as amended 76 Stat. 787, 21 U.S.C. 357(g)).

Dated: OCTOBER 3, 1966.

WINTON B. RANKIN,  
*Deputy Commissioner of Food and Drugs.*

[F.R. Doc. 66-10899; Filed, Oct. 5, 1966; 8:48 a.m.]



33 F.R. 818 (January 23, 1968)

*Food and Drug Administration***DRUGS FOR HUMAN USE CONTAINING RUTIN, QUERCETIN,  
HESPERIDIN, OR BIOFLAVONOIDS****NEW-DRUG APPLICATIONS**

The Food and Drug Administration published in the **FEDERAL REGISTER** July 9, 1966 (31 F.R. 9426), an announcement of the agreement by the National Academy of Sciences—National Research Council to assist the Food and Drug Administration in its review of the claims of effectiveness for the new drugs cleared between 1938 and October 10, 1962, on the basis of safety. Each holder of a new-drug application approved during that period was given an opportunity to present for the consideration of the reviewing experts the best data available to support the medical claims.

The Academy has submitted a report on a number of drugs containing rutin, quercetin, and citrus bioflavonoid compound. The Food and Drug Administration has considered the report and has concluded on the basis of the report and its own evaluations that there is no evidence that rutin, quercetin, hesperidin, or bioflavonoids are effective for use in man for any condition.

Under the Kefauver-Harris Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, lack of substantial evidence of effectiveness that a drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling is a basis for withdrawing approval of a new-drug application.

The Commissioner of Food and Drugs intends to publish a notice of opportunity for a hearing on a proposal to withdraw approval of all new-drug applications for drugs containing rutin, quercetin, hesperidin, or bioflavonoids alone and in combination with other drugs.

Promulgation of an order withdrawing approval of such new-drug applications will classify drugs containing any of these components as new drugs for which an approved new-drug application is not in effect. Any such drugs then on the market would be subject to regulatory proceedings. These components should also be withdrawn from dietary food supplements to avoid misbrandings.

Prior to initiating such action, however, the Commissioner of Food and Drugs invites all holders of new-drug applications which became effective under the new-drug provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505; 21 U.S.C. 355) for drugs containing rutin, quercetin, hesperidin, or bioflavonoids, and any persons who may be adversely affected by such action, to attend a meeting on January 31, 1968, at 1:30 p.m. in Room 804, Crystal Plaza No. 6, 2221 Jefferson Davis Highway, Arlington, Va. The purpose of the meeting will be to discuss the procedural matters involved in the proposed action of the Commissioner and to attempt to identify and resolve problems that may be anticipated as a result of the actions to be taken. Representatives who intend to participate in this meeting are asked to notify the agency in advance by writing to the Director, Bureau of Medicine, Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204, or calling his office (area code 703, 557-2686).

This announcement is made to give notice to interested persons of the proposed action and implementation of the NAS-NRC reports for the drugs listed above.

This statement is issued pursuant to the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050, as amended, 1052, as amended, 1055; 21 U.S.C. 352, 355, 371(a)) and delegated by him to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: JANUARY 15, 1968.

WINTON B. RANKIN,  
*Deputy Commissioner of Food and Drugs.*

[F.R. Doc. 68-811; Filed, Jan. 22, 1968; 8:45 a.m.]

## 21 C.F.R. 130.39

§ 130.39 New-drug status opinions; statement of policy.

(a) Over the years since 1938 the Food and Drug Administration has given informal advice to inquires as to the new-drug status of preparations. These drugs have sometimes been identified only by general statements of composition. Generally such informal opinions were incorporated in letters that did not explicitly relate all of the necessary conditions and qualifications

such as the quantitative formula for the drug and the conditions under which it was prescribed, recommended, or suggested. This has contributed to misunderstanding and misinterpretation of such opinions.

(b) These informal opinions that an article is "not a new drug" or "no longer a new drug" require reexamination under the Kefauver-Harris Act (Public Law 87-781; 76 Stat. 788-89). In particular, when approval of a new-drug application is withdrawn under provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act, a drug generally recognized as safe may become a "new drug" within the meaning of section 201(p) of said Act as amended by the Kefauver-Harris Act on October, 1962. This is of special importance by reason of proposed actions to withdraw approval of new-drug applications for lack of substantial evidence of effectiveness as a result of reports of the National Academy of Sciences—National Research Council on its review of drug effectiveness; for example, see the notice published in the FEDERAL REGISTER of January 23, 1968 (33 F.R. 818), regarding rutin, quercetin, et al.

(c) Any marketed drug is a "new drug" if any labeling change made after October 9, 1962, recommends or suggests new conditions of use under which the drug is not generally recognized as safe and effective by qualified experts. Undisclosed or unreported side effects as well as the emergence of new knowledge presenting questions with respect to the safety or effectiveness of a drug may result in its becoming a "new drug" even though it was previously considered "not a new drug." Any previously given informal advice that an article is "not a new drug" does not apply to such an article if it has been changed in formulation, manufacture, control, or labeling in a way that may significantly affect the safety of the drug.

(d) For these reasons, all opinions previously given by the Food and Drug Administration to the effect that an article is "not a new drug" or is "no longer a new drug" are hereby revoked. This does not mean that all articles that were the subjects of such prior opinions will be regarded as new drugs. The prior opinions will be replaced by opinions of the Food and Drug Administration that are qualified and current on when an article is "not a new drug," as set forth in Subpart D (proposed) of this Part 130.

33 F.R. 9908 (July 10, 1968)

*Food and Drug Administration*

[Docket No. FDC-D-112; NDA No. 5000 etc.]

**DRUGS FOR HUMAN USE CONTAINING RUTIN, QUERCETIN,  
HESPERIDIN, OR ANY BIOFLAVONOIDS**

**NOTICE OF OPPORTUNITY FOR HEARING ON PROPOSAL TO WITH-  
DRAW APPROVAL OF NEW-DRUG APPLICATIONS**

In an announcement published in the **FEDERAL REGISTER** of January 23, 1968 (33 F.R. 818), holders of new-drug applications for drugs containing rutin, quercetin, hesperidin, or bioflavonoids, and other interested persons, were invited to attend a meeting to discuss a proposal to initiate proceedings to withdraw approval of such applications. The meeting was held on January 31, 1968, at which time the Food and Drug Administration invited the submission of additional scientific, medical information that might be pertinent to the question of the effectiveness of these drugs. The additional information received, considered together with other information available, did not provide substantial evidence of effectiveness of such drugs for use in man for any condition.

Therefore, notice is hereby given to:

Abbott Laboratories.  
Arlington-Funk Labs. (Div. of U.S. Vitamin Corp.).  
Best Pharmaceuticals.  
The Blue Line Chemical Co.  
Brayten Pharmaceutical Co.  
The Central Pharmacal Co.  
Direct Labs., Inc.  
Grove Labs. (Subsidiary of Bristol-Myers).  
K-V Pharmacal Co.  
Lakeside Laboratories (Div. of Colgate-Palmolive Co.).  
Lemmon Pharmacal.  
Lloyd, Dabney & Westerfield, Inc.  
The Maltine Co.  
The S. E. Massengill Co.  
Merck Sharp & Dohme (Div. of Merck & Co., Inc.).  
Metro Med. Inc.  
Nadin Co.

Nysco Labs., Inc.  
 Organon, Inc.  
 The E. L. Patch Co. (now Smith, Miller & Patch, Inc.).  
 The Paul Plessner Co.  
 Physicians Drug & Supply Co.  
 Rexall Drug & Chemical Co.  
 Rhodes Pharmacal Co., Inc.  
 Richlyn Laboratories.  
 Robin Pharmacal Co.  
 E. R. Squibb & Son (Div. Olin Mathieson Chemical Corp.)  
 R. J. Strassenburgh Co. (Div. of Wallace & Tiernan, Inc.)  
 Table Rock Labs., Inc.  
 U.S. Vitamin Corp.  
 Walker Labs., Inc. (Div. of Richardson-Merrell).  
 Henry K. Wampole & Co.

and to any interested person who may be adversely affected, that the Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the following new-drug applications and all amendments and supplements thereto with respect to any drugs included in such applications which contain rutin, quercetin, hesperidin, or any bioflavonoid:

*New Drug Applications Deemed Approved for Drugs Containing Rutin, Quercetin, Hesperidin, or Bioflavonoids*

NDA No.	Drug name	Applicant's name and address
5000	Rutin Tablets.....	Abbott Laboratories, 14th and Sheridan Rd., North Chicago, Ill. 60061.
6020	Rutin Tablets; Rutorbin Tablets.....	E. R. Squibb & Sons, Division Olin Mathieson, Chemical Corp., 745 Fifth Ave., New York N. Y. 10022.
6070	Rutin Tablets.....	The Maltine Co., 745 Fifth Ave., New York, N. Y. 10022.
6156	Theoglycinate with Rutin and Phenobarbital.	Brayten Pharmaceutical Co., 1715 West 26th Street, Chattanooga, Tenn. 37400.
6291	Glytheonate with Rutin and Phenobarbital.	The E. L. Patch Co., now Smith, Miller & Patch, Inc., 902 Broadway, New York, N. Y. 10010.
6333	Synophyte Tablets.....	The Central Pharmacal Co., 116-128 East Third St., Seymour, Ind. 47274.
8200	Vir-I-Phyl.....	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 16900.

*New Drug Applications Deemed Approved for Drugs Containing Rutin, Quercetin, Hesperidin, or Bioflavonoids—Continued*

NDA No.	Drug name	Applicant's name and address
8036	Quertine (Queroctin, Abbott) .....	Abbott Laboratories, 14th Street and Sheridan Rd., North Chicago, Ill. 60600.
9074	Maxitate with Rauwolfia Compound Tablets. ....	R. J. Strassenburgh Co., Division of Wallace & Tiernan, Inc., 755 Jefferson Rd., Rochester, N. Y. 14603.
9118	Raufia Endote Tablets; Neo-Vir-I-Tin Encote Tablets. ....	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18900.
9123	Loten Tablets. ....	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18900.
9255	Wolfinez. ....	Lloyd, Daibney & Westerfield, Inc., 3941 Brotherton Rd., Cincinnati, Ohio 45209.
9455	Ruserp-C. ....	Lemmon Pharmacal, Temple Ave., Sellersville, Pa., 18900.
9588	Raulbexido Tablets. ....	K-V Parmacal Co., 2503 South Hanley Rd., St. Louis, Mo. 63144.
9657	Rubexanal with Reserpine. ....	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18900.
9005	Neo-Semhyten Capsules. ....	The S. E. Maasengill Co., 513-529 Fifth St., Bristol, Tenn. 37620.
9640	Ranwolfia Serpentina-Mannitol Hexanilate-Rutin Tablets. ....	Best Pharmaceuticals, 3725 Castor Ave., Philadelphia, Pa. 19124.
9681	Neo-Rauja Tablets. ....	Table Rock Labs., Inc., 812 Hampton Ave., Grersonville, S.C. 29601.
9685	Raufwolfia Serpentina-Mannitol Hexanilate-Rutin-Veratrum Viride Tablets. ....	Robin Pharmacal Co., 57 Hope St., Brooklyn, N. Y. 11211.
9691	Restolic Tablets; Restolic Forte Tablets. ....	Merck Sharp & Dohme, Division Merck & Co., Inc., West Point, Pa. 19476.
9914	Raumanultr-50 Tablets. ....	Nysco Labs., Inc., 34-24 Vernon Blvd., Long Island City, N. Y. 11101.
9945	C.V.P.; C.V.P. w/Vitamin K; Bivan Tablets; Duo-C.V.P. w/Vitamin K Capsules. ....	U.S. Vitamin Corp., 26 Vark St., Yonkers, N. Y. 10705.
10000	Tenserina Tablets (Spanish name); Tenserina Tablets (English name). ....	Abbott Laboratories, 14th and Sheridan Rd., North Chicago, Ill. 60604.
10013	"Bio-Flav" Citrus Bioflavonoid Complex and Vitamin C Tablets. ....	Nadin Co., 1813 Flower St., Glendale, Calif. 91201.
10046	Capilon Tablets. ....	The Paul Plesner Co., 635 30th Ave. North, Post Office Box 7087, St. Petersburg, Fla. 33734.
10063	Citroid Capsules. ....	Grove Labs., Subsidiary of Bristol-Myers, 8420 Delmar Blvd., Post Office Box 7300, St. Louis, Mo. 63177.
10114	Mannitrau Tablets. ....	Richlyn Laboratories, 3725 Castor Ave., Philadelphia, Pa. 19124.
10130	Rauman Tablets. ....	Direct Labs., Inc., 337 Genesee St., Post Office Box 708, Buffalo, N. Y. 14240.
10136	Routenal Tablets. ....	Physicians Drug & Supply Co., 1458 Chestnut Ave., Hillside, N. J. 07035.
10232	Flavoserp. ....	The Blue Line Chemical Co., 302 South Broadway, St. Louis, Mo. 63102.
10310	Prevolds. ....	Rhodes Pharmacal Co., Inc., 41 East Oak St., Chicago, Ill. 60611.
10572	Bioresp-C. ....	Henry K. Wampole & Co., 35 Commerce Rd., Stamford, Conn. 06902.
10816	Adrestat. ....	Organon, Inc., 375 Mount Pleasant Ave., West Orange, N. J. 07052.
11060	Bioscreen. ....	The Central Pharmacal Co., 116-128 East Third St., Seymour, Ind. 47274.

*New Drug Applications Deemed Approved for Drugs Containing Rutin,  
Quercetin, Hesperidin, or Bioflavonoids—Continued*

NDA No.	Drug name	Applicant's name and address
11051	Citroid Compound.....	Grove Labs., Subsidiary of Bristol-Myers, 902 Delmar Blvd., Post Office Box 720, St. Louis, Mo. 63177.
11052	Citroid Compound.....	Do.
11196	Citroid Jr.....	Do.
11214	Super Anagac Cough Syrup.....	Rexall Drug & Chemical Co., 3480 Beverly Blvd., Los Angeles, Calif. 90054.
11240	Serbio Capsules.....	Metro Med. Inc., 2510 South Blvd., Houston, Tex. 77006.
11474	Prednyl Tablets.....	Arlington-Funk Labs., Division of U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701.
11475	Prednis-C.V.P. Capsules.....	Do.
11057	Dacill-OR.....	Lakeside Laboratories, Division of Colgate- Palmolive Co., 1707 East North Ave., Mil- waukee, Wis. 53201.
12261	Natorexic Tablets.....	Walker Labs., Inc., Division of Richardson- Merrell, 1 Bradford Rd., Mount Vernon, N.Y. 10551.

It is proposed to withdraw approval on the grounds that there is a lack of substantial evidence that rutin, quercetin, hesperidin, or any bioflavonoid has the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof, or that such articles alone, or as added components with other drugs, are effective for use in man for any condition.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give each applicant and any interested person who would be adversely affected by an order withdrawing such approval an opportunity for a hearing at which time such persons may produce evidence and—arguments to show why approval of any new-drug application listed herein should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing any rutin, quercetin, hesperidin, or bioflavonoid to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days from the date of publication of this notice in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food and Drug Division,

Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing the approval of the new-drug application. Failure of such persons to file such a written appearance of election within 30 days following the date of publication of this notice in the FEDERAL REGISTER will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing by filing a timely written appearance of election, a hearing examiner will be named by the Commissioner and he shall issue a written notice of the time and place for the hearing.

This notice is issued under the authority contained in the Federal Food, Drug, and Cosmetic Act. (sec. 505, 52 Stat. 1052, as amended; 21 U.S.C. 355) and delegated to the Commissioner (21 CFR 2.120).

Dated: JUNE 28, 1968.

JAMES E. GODDARD,  
*Commissioner of Food and Drugs.*

35 F.R. 16332 (October 17, 1970)

*Food and Drug Administration*

[Docket No. FDC-D-112; NDA No. 9-965 etc.]

**DRUGS CONTAINING RUTIN, QUERCETIN, HESPERIDIN, OR ANY  
BIOFLAVONOIDS**

#### NOTICE OF WITHDRAWAL OF APPROVAL OF NEW-DRUG APPLICATIONS

On July 10, 1968, there was published in the FEDERAL REGISTER (33 F.R. 9908) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing ap-



proval of new-drug applications listed therein on the ground that there is a lack of substantial evidence that rutin, quercetin, hesperidin, or any bioflavonoid has the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof, or that such articles alone, or as added components with other drugs, are effective for use in man for any condition.

The firms listed below elected to avail themselves of the opportunity for a hearing. By letters of July 7, 1970, these firms were notified that their request for a hearing should be amended to comply with the regulations published in the **FEDERAL REGISTER** of May 8, 1970 (35 F.R. 7250) describing the scientific content of adequate and well-controlled clinical investigations and setting forth the procedural requirements for requesting public hearings and demonstrating that there is a genuine and substantial issue of fact that requires a hearing. Such amendment to the request for hearing has not been received. Counsel for U.S. Vitamin Pharmaceutical Corp. responded to the July 7, 1970 letter and requested a stay of any further proceedings in the proposal to withdraw approval of their new drug applications, citing pending litigation in the U.S. District Court for the Eastern District of Virginia and the U.S. District Court for the District of Delaware as grounds for delay. The fact that there is pending litigation does not provide sufficient grounds for the request, and the Commissioner concludes that further delay of the proposed withdrawal of approval is not justified.

NDA No.	Drug name	Applicant's name and address
9-965	C.V.P.; C.V.P. w/Vitamin K; Bivan Tablets; Duo-C.V.P. w/Vitamin K Capsules.	U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701.
11-474	Prednyl Tablets.	Arlington-Funk Labs., Division of U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701.
11-475	Prednis-C.V.P. Capsules.	Do.

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505 (e)), 52 Stat. 1053, as amended; (21 U.S.C. 355(e)), and under the authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing findings, approval of the above new-drug applications, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document.

Dated: OCTOBER 15, 1970.

SAM D. FINE,  
*Associate Commissioner for Compliance.*

[F.R. Doc. 70-14072 ; Filed, Oct. 16, 1970 ; 8:50 a.m.]

FEBRUARY 28, 1961.

Dr. Ralph G. Smith,  
Department of Health, Education & Welfare,  
Food & Drug Administration,  
New Drug Branch,  
Washington 25, D.C.

DEAR DR. SMITH: Attached herewith you will find a list of various effective New Drug Applications.

We should appreciate very much your advice with respect to the current status of these applications—that is, whether or not they are still considered to be “new drugs”.

Thank you for your kind cooperation in this matter.

Very truly yours

EPHRAIN GUNSBURG,  
*Assistant to the Vice President,*  
*U.S. Vitamin & Pharmaceutical Corporation.*

	NDA
Vi-Syneral Inj.....	6373
Vitamin A Inj. Vst., no longer marketed.....	6521
E-Toplex Inj., no longer marketed.....	6822
Aquasol A Parenteral.....	6823
Co-Salt .....	7150
Dodecavite .....	7152
Enelone, no longer marketed.....	7272
Enescorb, no longer marketed.....	7851
Methischol Inj.....	8326
Tisin, no longer marketed.....	8503
H.V.I. ....	8800
Stanone, no longer marketed.....	9002
Dilatol (Arlidin) Tablets.....	9367
Pantho-F .....	9794
Dilatol (Arlidin) Inj.....	9813
C.V.P. ....	9965
Dodecatriate, never marketed.....	11-004
Prednol .....	11-474
Prednis-CVP .....	11-475
DBI .....	11-624
Trypp .....	12-149
Emivan Tablets.....	12-451
Emivan Inj.....	12-452

NDA 9367 12452  
 9013 11475  
 11624 11474  
 12149 9794  
 12451 8099

U.S. Vitamin & Pharmaceutical Corporation  
 Attention: Mr. Ephrain Gunsberg  
 250 East 43rd Street  
 New York 17, New York

GENTLEMEN: This will acknowledge your letter of February 23, 1961, submitted personally by Mr. Ephrain Gunsberg on March 1, 1961, requesting our opinion on the new drug status of the products for which you hold effective new drug applications.

We are not furnishing a complete answer at this time. With respect to those products on which we are not replying, it is suggested that you submit a separate letter of inquiry on each one furnishing some information on marketing experience and enclosing five copies of your current labels and labeling, or if not marketed those which were previously used. On checking a number of the older applications, it is noted that final printed labeling was not submitted as requested in our "effective letters." Further, we are not sure that some products have been marketed—for example, E-Toplex Injection NDA 6322, Tisin NDA 8503 and Stanche NDA 9002.

The following products are still regarded as new drugs:

Arlidin Tablets.....	NDA 9367
Arlidin Injection.....	9813
DBI.....	11624
Trypp.....	12149
Emivan Tablets.....	12451
Emivan Injection.....	12452

In our opinion the following products are not new drugs when distributed under the labeling provided for in the respective effective new drug applications:

Prednis-CVR.....	NDA 11475
Prednyl.....	11474
Pantho-F.....	9794
M.V.I.....	8800

Copies of the final printed labels and labeling are requested for Pantho-F.

We will be pleased to comment on the other products if furnished with additional material as requested above.

Sincerely yours,

RALPH G. SMITH, M.D.,  
Director, New Drug Branch,  
Bureau of Medicine.

MAY 16, 1961.

Dr. RALPH G. SMITH  
U.S. Department of Health, Education, and Welfare  
Food and Drug Administration  
New Drug Branch  
Washington 25, D.C.

Re: N.D.A. No. 9965 C.V.P. Products

DEAR DR. SMITH: This is in reference to your letter of April 19, 1961 in response to our letter of February 28, 1961 concerning the new drug status of C.V.P. products.

In accordance with your request, we are submitting herewith five (5) copies of the labels and labeling currently being used for these products, which we have been marketing continuously for at least ten years.

It is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective.

We should appreciate very much your confirmation of the above.

Thank you for your kind cooperation in this matter.

Very truly yours,

LOUIS FREEDMAN, Ph.D.,  
Vice President in Charge of Research,  
U.S. Vitamin & Pharmaceutical Corporation.

U.S. VITAMIN & PHARMACEUTICAL CORPORATION,  
800 Second Avenue, New York 17, N.Y., October 5, 1965.  
Department of Health, Education, and Welfare  
Food and Drug Administration  
Washington, D.C. 20204

Attention: George P. Larrick, Commissioner of Food and Drugs.

DEAR MR. LARRICK: This is in reference to your letter of May 27, 1965, requesting information under the reporting re-

quirements of Section 130.35 of the Regulations for the following products:

1. Pantho-F Cream, 0.2%
2. Pantho-F Cream, 1%
3. C.V.P. with vitamin K Tablets
4. C.V.P. with vitamin K Syrup
5. Prednis—C.V.P. Capsules

In view of the subsequent correspondence between Joseph Stetler, Esq., of the Pharmaceutical Manufacturers Association, and yourself, and our desire to submit promptly any information which we believe will be useful in your evaluation of the above-identified products, we have carefully reviewed our files. In our opinion, there is nothing in them which reveals that the products are not safe and effective for the purposes for which they are marketed.

This information is being submitted without prejudice to our position that you do not have the legal authority to require reports with respect to drugs which are no longer "new drugs", and the submission of the above information does not constitute any implied admission as to the legal status of the products concerned.

Very truly yours,

EPHRAIM GUNSBERG,  
Vice President, Technical Operations,  
U.S. Vitamin & Pharmaceutical Corporation.

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LAW OFFICES. WALD, HARKRADER, NICHOLSON & ROSS,  
1320 Nineteenth Street, N.W., Washington, D.C. 20036,  
August 7, 1970.

Re: Dkt. No. FDC-D-112.

CHARLES C. EDWARDS, M.D.  
Commissioner of Food and Drugs  
Food and Drug Administration  
Department of Health,  
Education and Welfare  
Parklawn Building  
Rockville, Maryland 20850

DEAR DOCTOR EDWARDS: USV Pharmaceutical Corporation, holder of three new drug applications involved in the captioned proceeding (Nos. 9665, 11-474 and 11-475), has re-

ceived your letters of July 7, 1970. We understand those letters to require compliance with the "Hearing and Scientific-Content Regulations", published last May 8, (35 Fed. Reg. 7250), as a predicate to a hearing on the Commissioner's proposal of July 10, 1968 to withdraw approval of those NDA's. The company requests a stay of all further proceedings herein as to these NDA's for the following reasons:

1. There is no need for *any* proceedings as to these NDA's if the products alleged by FDA to be "covered" thereby are not new drugs. That issue is now pending for judicial determination on cross-motions for summary judgment in *USV Pharmaceutical Corp. v. Richardson, et al.*, Civil No. 4915-A in the United States District Court for the Eastern District of Virginia. The motions have been fully briefed. In the course of a pretrial conference on July 17, 1970, the Court ruled that whether the suit can be disposed of on the motions will shortly be decided, and that any trial which may be found necessary will in any event be held on October 23, 1970. The new-drug status of the products alleged by FDA to be "covered" by the company's three NDA's will thus be judicially determined within the next few months.

2. The validity of the May 8 "Hearing and Scientific-Content Regulations" is already before the United States District Court for the District of Delaware in *Pharmaceutical Mfrs. Ass'n v. Richardson, et al.*, Civil No. 3946. We believe that for the reasons alleged by PMA the May 8 regulations are invalid, and that in any event it would be inappropriate to apply them to the pending proceeding, in which all prerequisites to a hearing then in force were fully met as long as two years ago. This latter issue need not be reached, however, if the May 8 regulations are invalid as alleged in the pending litigation.

Orderly accommodation of judicial and administrative authority thus requires that all proceedings as to the NDA's involved in this proceeding be stayed. The stay should continue at least until the issues before the Virginia and Delaware courts are resolved.

USV requests that if a stay is denied the company be given at least thirty days from receipt of notice of the denial to file a further response to your letters of July 7. The company further requests that all communications in this proceeding be addressed to this firm as its counsel of record in compliance with 5 U.S.C. § 500(f).

This letter is without prejudice to the company's position that in the event of administrative adjudication with respect to these NDA's you may be disqualified from participating in the decision by reason of having pre-judged the issues, as evidenced by statements and allegations advanced in the defense of *USV Pharmaceutical Corp. v. Richardson, supra*.

We should appreciate an opportunity to meet with you at your early convenience to discuss this proposal for a stay and the future course of these proceedings.

Respectfully submitted,

WALD, HARKRADER,  
NICHOLSON & ROSS  
ROBERT L. WALD,

*Counsel for USV Pharmaceutical Corporation.*

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DEPARTMENT OF HEALTH,  
EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
WASHINGTON, D.C. 20204,  
October 14, 1970.

Mr. Robert L. Wald  
1320 Nineteenth Street, N.W.  
Washington, D.C. 20036

DEAR MR. WALD: This replies to your letter of August 7, 1970, in response to ours of July 7, 1970, in which you request a stay of all further proceeding involving your client's new drug applications 9965, for C.V.P., C.V. with Vitamin K, Bivam Tablets, and Cuo-C.V.P. with Vitamin K Capsule 11-474 for Prednyl Tablets; and, 11-475 for Prednis-C.V.P. Capsules.

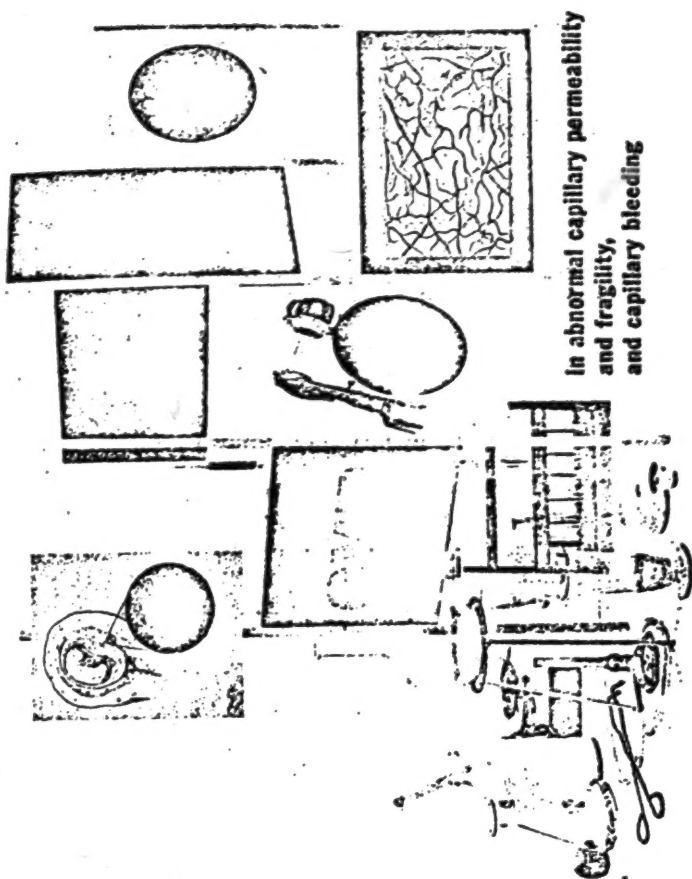
We regard these products as new drugs as defined in the Federal Food, Drug, and Cosmetic Act. Our letter of July 7, 1970, suggested the request for a hearing be amended within 30 days from receipt of that letter, by submitting a well-organized and full-factual analysis of clinical and other investigational data that USV Corporation is prepared to prove in a hearing, setting forth specific facts showing that it is a genuine and substantial issue of fact that requires a hearing. To date, no amendment has been received.

Accordingly, we conclude that no useful purpose will be served by delaying the processing of a final order to withdraw approval of the subject new drug applications. The pending litigation in the United States District Court for the Eastern District of Virginia and the United States District Court for the District of Delaware do not provide sufficient grounds to further delay these proceedings.

Your request for a 30-day extension, in the event of our denial of a stay, is also denied.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,  
*Commissioner of Food and Drugs.*





*Exclusive Water-Soluble Citrus Bioflavonoid Compound\**  
*With Ascorbic Acid*

**"THE INTEGRITY OF THE CAPILLAARY SYSTEM IS AN ESSENTIAL  
 FACTOR IN HEALTH AND DISEASE."**<sup>18</sup>

The state of the capillary walls with respect to permeability is "of the utmost importance in maintaining the nutrition of the tissues and in maintaining the normal distribution of fluids within and without the vascular system."<sup>17</sup> Complex vital processes are dependent on the functional health of these minute blood vessels.

The capillary wall is a single layer of endothelial cells bound together by an intercellular cement, with millions of pores which serve as selective sieves for plasma. The normal capillary wall is impermeable to serum albumin and serum globulin. In certain pathologic conditions, these pores enlarge, permitting the passage of larger protein molecules (increased capillary permeability) and, in certain later stages, the cement may be so weakened as to cause a rupture of the vessel (capillary fragility).<sup>18</sup>

In diabetes, hypertension, threatened and habitual abortion, purpuras, epistaxis, viral and bacterial infections, periodontal diseases, peptic ulcer and other conditions, abnormal permeability and fragility of capillaries frequently occur.<sup>8 9 12 15 16</sup> Many drugs (e.g., antibiotics, sulfonamides, isoniazid, certain steroids, analgesics and antiarthritics), numerous commonly used chemicals, as well as viruses and bacterial toxins increase capillary permeability and fragility.<sup>10 20</sup>

#### CAPILLARY FRAGILITY WIDESPREAD

In apparently healthy subjects a progressive increase in capillary fragility is common after age 20 and extreme fragility occurs in 80 per cent of individuals past 60.<sup>7</sup> All hypertensive diabetics of a large series showed increased capillary fragility.<sup>11</sup> Abnormal capillary fragility was found in 80 per cent of patients with rheumatic fever,<sup>19</sup> in 90 per cent with spontaneous purpura, in 49 per cent of allergic patients,<sup>20</sup> in 60 to 80 per cent of habitual aborters.<sup>10 11</sup> Injury to the capillary system has been reported in various infections; e.g., viral hepatitis, poli-

\*Made by an exclusive patented process.

myelitis, smallpox, measles, mumps, rabies, influenza, common cold, encephalomyelitis and primary atypical pneumonia.<sup>14</sup>

### PERMEABILITY

#### HOW C.V.P. HELPS OVERCOME ABNORMAL CAPILLARY PERMEABILITY

C.V.P. is a water-soluble biologically active flavonoid compound from citrus peel and pulp combined with ascorbic acid. C.V.P. acts to maintain the integrity of capillary walls by strengthening the intercellular ground substance or cement which binds together the endothelial cells.<sup>16</sup> This helps to increase capillary integrity and aids in preventing and overcoming abnormal capillary permeability, fragility, and bleeding. The water-soluble bioflavonoid compound of C.V.P. is, by itself, highly active in a number of biological and chemical tests. Clinically, in the correction of capillary fault, certain bleeding states do not respond to vitamin alone, but do respond to the combination of bioflavonoids and ascorbic acid.<sup>16</sup>

### PHYSIOLOGIC EFFECTS OF C.V.P.

The physiologic properties of the bioflavonoids (biologically active flavonoids) have been extensively investigated. While the various mechanisms are not yet completely understood, these physiologic actions have been demonstrated:

1. *Anti-hemorrhagic effect.*—In experimental studies, the water-soluble bioflavonoid complex available exclusively in C.V.P. protected against the capillary fragility and hemorrhage-producing effects of bacterial polysaccharide in tumor-bearing rats.<sup>2 45</sup> Clinically, the anti-hemorrhagic effect of C.V.P. has been demonstrated in such bleeding conditions as habitual abortion,<sup>31</sup> retinitis,<sup>8</sup> bleeding duodenal ulcer and ulcerative colitis,<sup>21 39</sup> epistaxis,<sup>44</sup> purpuras,<sup>3 39</sup> tonsillectomy bleeding and other otolaryngologic procedures,<sup>21 44</sup> periodontal disease,<sup>25 26</sup> hemorrhagic diatheses.<sup>3</sup>

2. *Anti-inflammatory effect.*—C.V.P.'s water soluble complex is actively anti-inflammatory. It definitely inhibits the proteolytic action giving rise to such substances as histamine and leukotaxine which produce the abnormal capillary permeability associated with inflammation.<sup>2 4 30</sup>

3. *Inhibition of hyaluronidase.*—The "spreading factor," which might cause increased capillary permeability, acts to

dissolve the intercellular cement substance. Bioflavonoids in combination with ascorbic acid markedly inhibit the activity of this enzyme.<sup>36</sup>

4. *Inhibition of histamine.*—Several investigators have postulated that bioflavonoids have an antianaphylactoid action. Among them is Ungar<sup>37</sup> who showed that bioflavonoids inhibit release of histamine from blood cells.

5. *Decreases excessive bleeding time* when this is due to increased capillary permeability.<sup>37</sup>

6. *Virus inhibitory.*—In vivo and in vitro experiments indicate that the water-soluble bioflavonoid complex of C.V.P. may have anti-viral activity.<sup>44 45</sup>

7. *Relationship between bioflavonoids and ascorbic acid.*—Bioflavonoids increase the retention of ascorbic acid in the blood and adrenal glands of experimental animals.<sup>44</sup> Patients with certain types of capillary hemorrhage respond better to a combination of the bioflavonoids and ascorbic acid than to ascorbic acid alone.<sup>46</sup> The water-soluble citrus bioflavonoids (C.V.P.) have been reported to prevent scurvy in patients placed experimentally on a low ascorbic acid diet.<sup>41</sup>

#### C.V.P. IS AN EXCLUSIVE COMPOUND—SUPERIOR TO HESPERIDIN, RUTIN

C.V.P. is different from other flavonoid products. Only C.V.P. provides the many active water-soluble bioflavonoid factors of the whole citrus bioflavonoid complex. C.V.P. (due to special processing) is relatively low in hesperidin, naringin and other comparatively insoluble and inactive flavonoids found in citrus.

"The very low solubility of hesperidin and rutin in water is sufficient to explain their relatively low activity by the oral route." \* Hesperidin, naringin, and certain other water-insoluble flavonoids are inactive in biologic tests in which C.V.P. is highly active.<sup>4 30 45</sup> Present evidence in our laboratories supports the view that the apparent activity of certain preparations containing hesperidin given orally is due to traces of active flavonoids

which may accompany the insoluble hesperidin. As demonstrated in laboratory experiments, C.V.P. has a many times greater effect than rutin in maintaining capillary integrity.<sup>3, 48</sup>

#### CLINICALLY TESTED, SAFE, WELL TOLERATED

Laboratory and clinical investigations with C.V.P., starting in 1946, have demonstrated its high degree of safety and its value in restoring and maintaining capillary integrity. C.V.P. is well tolerated and free from side effects, even when given continuously for long periods.





TO HELP CORRECT FAULTY CAPILLARY PERMEABILITY AND FRAGILITY AND RESTORE CAPILLARY INTEGRITY . . . AND THUS AID IN PREVENTING AND CHECKING CAPILLARY BLEEDING, AND NORMALIZING CAPILLARY FLUID INTERCHANGE IN . . .

HABITUAL AND THREATENED ABORTION; POSTPARTUM BLEEDING

Three out of every four habitual aborters treated with C.V.P. from early pregnancy successfully delivered normal, healthy infants.<sup>31,46</sup> Two out of every three threatened aborters were enabled, on C.V.P. treatment, to complete gestation and deliver live, healthy babies. "There was a decrease in postpartum bleeding in the series of treated patients as compared with nontreated patients."<sup>31</sup>

#### EPISTAXIS, OTOLARYNGOLOGY, TONSILLECTOMY

C.V.P., or C.V.P. with vitamin K, produced a "decided decrease in oozing" after the surfaces were cut in tonsillectomies and adenoidectomies; "a sharp decrease in the number of nose-

bleed recurrences" in epistaxis; rapid reduction of swelling and postoperative discoloration in rhinoplasties, otoplasties, septal resections and other otolaryngologic surgery; "encouraging results" in the treatment of acute serous otitis.<sup>24</sup> In patients with epistaxis, C.V.P. with vitamin K "almost invariably prevented recurrences." <sup>44</sup>



#### PURPURA, ECCHYMOSIS

In patients under treatment with corticosteroids, C.V.P. may be effective in protecting against or overcoming purpura, ecchymosis and other manifestations of capillary fault commonly resulting from prolonged steroid therapy.<sup>33</sup> C.V.P. helps prevent and arrest capillary hemorrhage associated with non-thrombocytopenic purpura.<sup>8</sup>

#### HYPERTENSION

Abnormal capillary permeability and fragility occur in many hypertensives and may lead to retinal hemorrhage and other

vascular accidents.<sup>1</sup> C.V.P. helps to increase capillary resistance and thus may act to prevent these complications.\*

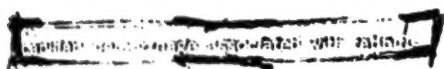
#### "LITTLE STROKES"

Accepting the biological premise that capillary injury and capillary hemorrhage play an important role in "little strokes," a group of investigators<sup>32</sup> treated with C.V.P. a small series of 13 patients who had had one to four previous "little strokes." In this preliminary report there was no further occurrence of "little strokes" in 10 cases during the one to three years of therapy.

#### DIABETIC RETINITIS, OCULAR DISORDERS

"C.V.P. provides the ophthalmologist with a valuable therapeutic aid in the management of certain ocular diseases . . . in which increased capillary fragility and permeability are the principal or complicating factors" (diabetic and hypertensive retinopathies, central angiospastic retinopathy, vitreous opacities, macular degeneration). It results in "more rapid clearing of hemorrhages, when present, and improvement in visual acuity."<sup>33</sup>

C.V.P. may help protect the retinopathy-prone diabetic or hypertensive from developing this all-too-frequent vascular complication.\*<sup>9</sup>





**BLEEDING GUMS, GINGIVITIS, PYORRHEA, PERIODONTAL CONDITIONS**

In chronic gingivitis, chronic pyorrhea and periodontosis—often in cases of long duration and unresponsive to other therapy—"the salutary effect (of C.V.P.) was evident and often dramatic."<sup>26,27</sup> C.V.P. "can be used very effectively" as preventive or inhibitory therapy in known or potential hemorrhagic cases.<sup>28</sup>

**MENORRHAGIA**

C.V.P. helps reduce bleeding in menorrhagia and metrorrhagia.<sup>46</sup>

**RH INCOMPATIBILITY**

A small number of Rh negative women, who had previously delivered erythroblastotic infants, were started on C.V.P. before the 14th week of pregnancy. No significant rise in antibody titer was observed. All babies were born alive, healthier and either not affected, or less affected, than those of previous births.<sup>22,32</sup>

**CERTAIN RESPIRATORY CONDITIONS**

Significant ameliorative effects were obtained with C.V.P. in colds, influenza and certain other respiratory infections.<sup>12,13</sup> "Our results strongly suggested that the bioflavonoids operate in the infections, at least in part, by restoring normal capillary integrity."

Investigators,<sup>42,43</sup> who employed C.V.P. therapeutically in industrial plants, reported symptomatic relief in the common cold and other respiratory infections and impressive reduction in absenteeism.

**RHEUMATOID ARTHRITIS**

Clinical studies<sup>33,38-45</sup> suggest that C.V.P. has a salutary effect on the capillary syndrome in the affected areas in rheumatoid arthritis and acute bursitis. C.V.P. is "a valuable adjunct in the management of rheumatoid arthritis" and is particularly helpful in preventing purpura and other evidence of capillary damage resulting from corticosteroids.<sup>33</sup>

**HEMORRHAGIC DUODENAL ULCER AND ULCERATIVE COLITIS**

Uncomplicated hemorrhagic duodenal ulcer and ulcerative colitis responded to treatment with C.V.P. in a most satisfactory manner. Bleeding was arrested within a few days.<sup>21,39</sup>

**HEMORRHAGIC CYSTITIS**

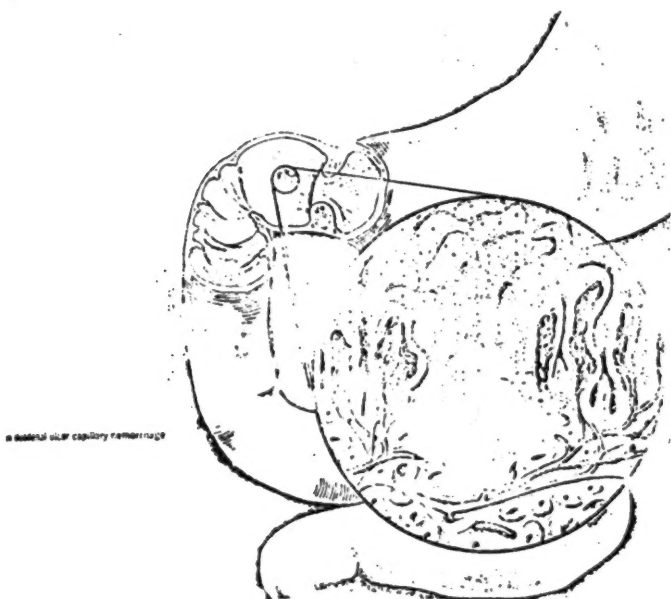
In a preliminary study, C.V.P. was found to check bleeding and inflammation in hemorrhagic cystitis by acting to reduce abnormal capillary permeability and fragility. Symptomatic relief was rapid and pathogenic organisms disappeared from the urine within five days.<sup>23</sup>

**POSTOPERATIVE BLEEDING**

Administered pre- and postoperatively, C.V.P. had a salutary effect on capillary bleeding and hastened healing following surgical procedures.<sup>8,24</sup>

**RADIATION THERAPY**

C.V.P. helps protect against capillary damage due to radiation and minimizes radiation erythemata. Does not reduce sensitivity of malignant tissue to x-ray irradiation.<sup>12</sup>



a lateral view of capillary hemorrhage

*safe, simple, effective,  
in the control of  
abnormal capillary permeability,  
fragility and  
resultant bleeding*

**AVIP**

Each C.V.P. capsule, or 5 cc.

contains: 1 (vitamin) synth. product:

CITRUS BIOFLAVONOID COMPOUND\* . . . . . 100 mg.

ASCORBIC ACID (Vitamin C) . . . . . 100 mg.

**100-C.V.P.**

*For use in patients in whom low prothrombin levels may  
concomitantly abnormal capillary permeability and fragility.*

Each 0.5 G.P. with Vitamin K tablet, or 5 cc.

contains: 1 (vitamin) synth. product:

CITRUS BIOFLAVONOID COMPOUND\* . . . . . 100 mg.

ASCORBIC ACID (Vitamin C) . . . . . 100 mg.

MENADIOLONE (Vitamin K) . . . . . 0.50 mg.

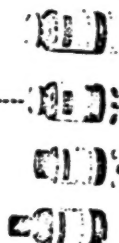
\*Original and exclusive (patented) compound containing the many active  
water-soluble factors of the whole natural citrus fruit.  
Readily absorbed (from its special processing) of heparin, streptogen and other  
comparatively insoluble and inactive flavonoids found in citrus.

**capsules**

0.5 G.P. - Contains of 100, 100 and 1000 tablets; 4 cc., 10 cc. and 100 cc. syringes.

100-C.V.P. - Contains of 10, 100, 500, and 1000 tablets.

0.5 G.P. with Vitamin K - Contains of 100 and 1000 tablets; 4 cc., 10 cc. and 100 cc. syringes.





Note: The active ingredients of this product are calcium, vitamin P, and vitamin K. These vitamins and minerals are important for the maintenance of blood vessels.

	In divided doses daily...		
	C. V. P. (capsules or 100 drops)	Calc-V. P. (capsules)	C. V. P. with Vitamin K (100 drops)
adults For the prevention or treatment of abnormal capillary permeability and fragility, and capillary bleeding in... hypertension, diabetes, retinal hemorrhage, prevention of "little strokes", purpura, rheumatoid arthritis	3 to 6 3 to 12 3 to 6	2 to 3 2 to 6 2 to 3	3 to 6 — 3 to 6
habitual abortion, Rh incompatibility bleeding in pregnancy, threatened abortion	9 to 15 9 to 15	5 to 8 5 to 8	9 to 15 9 to 15
urinary and enteric hemorrhage (cystitis, duodenal ulcer, colitis), bleeding gums, epistaxis, gingivitis, pyorrhea, periodontal conditions	6 to 12 6 to 9	3 to 6 3 to 5	6 to 12 6 to 9
surgery, x-ray treatment (for one week prior to surgery or x-ray treatment, during x-ray therapy and convalescence) "common cold", certain virus and respiratory conditions	6 9 to 12 for two days 6 for next two or more days	3 4 to 6 for two days 3 for next two or more days	6 — —
maintenance dose to prevent recurrence of capillary damage	1 to 3	1 to 2	—
children therapeutic dose in treatment of increased capillary permeability and fragility, and capillary bleeding tonsillectomy, other surgery (5 to 10 days before and for a like period following surgery)	3 to 6 3 to 6	2 to 3 2 to 3	3 to 6 3 to 6
maintenance dose	1 to 3	1 to 2	—



In the United States District Court, for the Eastern  
District of Virginia

[Caption omitted]

*Deposition of Theodore H. Spaet, a witness, taken by plaintiff pursuant to subpoena duces tecum dated August 28, 1969, at 245 Park Avenue, New York, N.Y., 10017, on September 4, 1969 at 10:00 a.m. before Charles Richer, a Shorthand Reporter and Commissioner of Deeds of the City of New York*

[2]

APPEARANCES

Messrs. Wald, Harkrader & Rockefeller, Attorneys for plaintiff, 1225 Nineteenth Street, NW., Washington, D.C.

By: Joel E. Hoffman, Esq., Miss Selma M. Levine, Robert L. Wald, Esq., Of Counsel.

Joanne S. Sisk, Esq., and Lillian Scott, Esq., Attorneys for Food, Drugs & Environmental Health Division, Office of General Counsel, United States Department of Health Education and Welfare, Washington, D.C.

J. Joseph Belson, Esq., Assistant to the Director, Division of Case Guidance, Bureau of Compliance, U.S. Food and Drug Administration, 200 C Street, SW., Washington, D.C.

Also present: Dr. Harvey S. Sadow.

[Theodore H. Spaet, called as a witness by plaintiff, having been first duly sworn by a Commissioner of Deeds of the City of New York, testified as follows:]

Examination by MR. HOFFMAN:

Q. Dr. Spaet, I wonder if you could give us your full [3] name, again, for the record?

A. Middle initial or full?

Q. The middle initial will suffice.

A. Theodore H. Spaet.

Q. And your address?

A. 23 Rectory Lane, Scarsdale, New York.

Q. Are you here today pursuant to a subpoena?

A. I am.

MR. HOFFMAN. Mr. Reporter, I would like you to mark the subpoena as Deposition Exhibit 1 for identification.

(Subpoena dated August 28, 1969, addressed to Dr. Theodore H. Spaet, 23 Rectory Lane, Scarsdale, N.Y., marked Plain-

tiff's Exhibit 1 for identification as of this date.)

Mr. HOFFMAN. I suppose the record should show that there is attached to Exhibit 1 a single-page schedule listing documents.

Q. Dr. Spaet, I show you Exhibit 1. Can you tell me if this is the subpoena to which you just referred?

A. It is.

Q. Doctor, what is your occupation?

A. Physician.

Q. Are you a practicing physician or a teaching phy [4] sician or both?

A. A description of my situation, I think, would be a full-time employee of Montefiore Hospital in the Albert Einstein College of Medicine, and my job is to run the Department of Hematology at Montefiore Hospital and also to serve on the faculty of the College.

Q. Is your official title Chairman of the Department?

A. No, my title is Head.

Q. Dr. Spaet, have you been a member of a panel established by the Drug Efficacy Study of the National Academy of Sciences' National Research Council?

A. I presume this is the proper nomenclature. If it is, I was.

Q. It is. I am sure Mrs. Sisk will tell you if it is not.

Dr. Spaet, did you bring with you any documents pursuant to the subpoena, Exhibit 1?

A. I did.

Q. May I see them, please?

A. Yes (handing). Those are the ones I brought.

Mr. HOFFMAN. Let the record show that Dr. Spaet has handed me ten documents, each consisting of several pages, some typed, some printed and some Xeroxed copies [5] of other documents.

Off the record, please.

(Discussion off the record.)

Mr. HOFFMAN. On the record, please.

Counsel for the defendants have agreed to dispense with reading the title of each of the documents brought by the witness. A list of those documents will be supplied to the reporter for marking as Exhibit 2 for identification.

Let the record also show that Mrs. Sisk has handed me four additional documents brought by her rather than the witness.

A list of those documents will be supplied and attached as Exhibit 3.

By Mr. HOFFMAN:

Q. Dr. Spaet, of the ten documents which you have brought with you, nine appear to be reprints of medical literature.

I wonder if you can tell us what they are, in general, and how they fit under the schedule?

A. These are two categories of paper. One is essentially a review of the literature and an editorial of evaluation of the bioflavonoids, and the other is the original papers reporting clinical results.

Q. By an evaluation of the bioflavonoids, are you [6] referring to a document headed "Drug Efficacy Study, Form A"?

A. No, I am referring to the report of the Council on Pharmacy and Chemistry of the American Medical Association.

That was in the way of an evaluation.

I am referring just merely—not to the ones that are the official forms that were given to us, but to the reprints.

Q. Is the report to the Council on Foods and Nutrition the one that was published in 1957?

A. Yes, it is.

Q. Can you tell us, Dr. Spaet, under what portion of the schedule these documents fell and why you brought them?

A. Well, it was my understanding, in interpreting the material, that any relevant material in our discussion today should be brought.

Q. What do you mean by "our discussion today," Doctor, so we have it on the record?

A. Well, I presumed we were going to discuss the FDA recommendation with respect to the bioflavonoids.

Q. When you received the subpoena, Dr. Spaet, did you personally search any files that are in your possession?

A. I did.

[7] Q. Are these all of the documents that you find in the files that you believe fell within the scope of the subpoena?

A. Yes, sir.

Q. I believe you mentioned, and it may have been during an off-the-record colloquy, that there were other documents relating to the products, other than those manufactured by USV Pharmaceutical Corporation, but that you did not bring those; is that correct?



A. That's correct.

Mrs. SISK. Those are the documents which I brought.

Mr. HOFFMAN. I see.

By Mr. HOFFMAN:

Q. Dr. Spaet, are you familiar with the documents produced by Mrs. Sisk?

A. Yes.

Q. Are those the only documents relating to the products of USV, which were in your files, to which you referred?

A. I would not be able to answer that without consulting my files.

Q. I wonder, Dr. Spaet, if you would check your files on that point and let me know in a letter the results of your further checking?

[8] A. Certainly. I think what you should do is provide me with some sort of reminder in writing.

Q. I certainly will. We will confirm this by letter after this deposition.

A. Thank you.

Q. Dr. Spaet, have you ever had other documents in your possession that fell within the scope of this subpoena, but which you do not have?

A. Yes.

Q. Could you describe those generally, please, and tell us also why you do not have them?

A. Yes, sir. In preparing our statement to the FDA we went through a certain amount of material, made notes, had a general statement of the material that we were to present, which we brought in in a rough form to meetings that we held, and these were not kept by us.

Q. These were notes of the meetings and notes of the thoughts of the panel members during this consideration of bioflavonoid products?

A. I did not—in my own possession—have notes of the meetings, but there was other material.

For example, we used as a basis for our decision—this is by no means an exhaustive list of it, it is just what I had in my file.

[9] Q. What happened to the rest of it?

A. I don't know. We left it at the buildings where the meetings were held. I don't remember the details.

Q. I thought you said, Doctor, there were some notes as to the meetings and notes as to the thoughts of the panel members.

You say you did not have such notes in your possession at any time?

A. Well, can we go off the record a minute?

Mr. HOFFMAN. Sure. Off the record.

(Discussion off the record.)

Mr. HOFFMAN. On the record, please.

Q. Just to close up on this one subject, Dr. Spaet, who made the notes to which you have referred? Were they your notes or notes someone else made?

A. There are two categories of notes, notes I made myself and notes made by other panel members, including Dr. Middleman.

Q. Was he classified as a panel member?

A. He was executive secretary of the panel. He also made notes.

Q. But the notes you made were left on the table at the conclusion of the meetings?

A. Either that or destroyed in my own home or my own [10] office, which I think would be included.

Mr. HOFFMAN. Thank you, very much, Dr. Spaet.

Miss Levine will continue on related subjects.

By Miss LEVINE:

Q. Dr. Spaet, are you in private practice at all or is your time spent primarily in research?

A. If you say "at all," the answer has to be yes. I am in private practice to the extent that occasionally if a case that is particularly in my domain is brought to the attention of our staff, I will see such a patient, and occasionally I am called as an outside consultant, but this is a rare event.

Q. What proportion of your time would you say is spent in research?

A. In research?

Q. Teaching and private practice, each of those.

A. I would say half in research and the remainder in, let's say 30 percent in teaching and—

Q. So the private practice is small?

A. Negligible.

Q. Are you certified by a specialty board?

A. Yes.

Q. Would you state which one?

A. The Board of Internal Medicine.

[11] Q. Would you state what the specialty of hematology is?

A. Yes, it generally covers the blood and its disorders.

Do you want more detail?

Q. A little.

A. There are, I would say, four categories of hematology. One is the general problem of the white cell, one is the general problem of the red cell, and one is the general problem of the third type of blood cell called the platelet, and the fourth are the plasma proteins involved in blood coagulation.

Q. Does hematology concern itself with the structure function and the pathology of the vasculature?

A. That is a gray area, in the sense that I would say most hematologists have not been concerned with this but a few, and I would say a few of us have considered this an important component of hematology, since some of the blood components interact.

Q. What would that specialty be called that is confined specifically to the vasculature?

A. Let's go off the record.

Mr. HOFFMAN. Off the record, please.

(Discussion off the record.)

[12] Mr. HOFFMAN. On the record, please.

A. [Continuing.] You have raised an extremely complex question.

I have just finished writing a paper that I am going to present in a few weeks in Helsinki, in which the conclusions that this particular interaction between the hematology domain and the blood vessel is not as yet a discipline and that many people are doing isolated pieces of research in it, and it is high time they got together.

I think at this stage of the game the specialty of the blood vessel and the kind of reaction we are talking about is really not as yet defined.

Q. What is the nature of the research that you have conducted in medicine?

A. The general word that describes it is hemostasis.

Q. Would you describe that?

A. Hemostasis means the ability of the blood components that are responsible for stopping bleeding, the ability of these components to react normally and also abnormally.

On the one hand they don't work sufficiently so that bleeding results, and on the other hand they react inappropriately so that thrombosis results.

Q. Did any of this research that you have conducted concern itself with the vascular function of pathology?

[13] A. Yes.

Q. Can you say what that was?

A. Yes. In approximately 1950 I published my first major paper, which was entitled "Vascular Factor in the Pathogenesis of Hemorrhagic Syndromes."

I am quoting this title from memory of a paper I wrote some—almost twenty years ago.

The thrust of this paper was that when certain components of the hemostatic system, that is, platelets and blood coagulation are abnormal, the blood vessel suffers.

This is a concept which has been reviewed since 1959, and it is now the subject of the major work of the Thorndyke Laboratories.

Q. Have you carried out any further investigation in that area?

A. Our most recent area of interest is on the other side of the coin, as I mentioned. We are studying the type of disease that leads to thrombosis, the concept being that thrombosis is a blood vessel type of disease.

Q. Have you ever used CVP clinically or in any research?

A. No, I have not.

Q. Do you know if any member of the panel has used CVP in research or practice?

[14] A. I do not.

Q. Dr. Spaet, are you familiar with the guidelines that were set down for the panel on drugs used in hermatology disorders for all of the panel of the NASRC?

A. To the best of my memory.

Q. Would you describe generally what those guidelines covered?

A. Yes. It was our mission, as I read and understood it, that we were to ascertain whether a drug, first of all, was efficacious and, secondly, whether there was any toxicity associated with the use of this drug that outweighed its efficacy and, thirdly, whether in any combination the added ingredient contributed to the efficacy of the combination, and fourthly, in general, that the burden of establishing efficacy rested upon the people who were marketing the drug.

Q. Do you recall what criterion was applied in determining whether a particular product was considered effective?

A. Do you mean how we came about arriving at this decision?

Q. Yes.

A. Yes.

Q. In general.

A. In general, yes. In general the major literature [15] on the subject was covered by us and our own breakdown and experience were added to it to produce what I suppose might be considered a new ingredient.

In some cases—to clarify that a little bit, in some cases the value judgment might not have been in the original publication, but adding together a series of publications without value judgments, our professional judgment was made and then the source of our decision.

Q. There was a panel on cardiovascular diseases; was there not, Dr. Spaet?

A. As far as I know.

Q. Was there a panel on obstetrics and gynecology?

A. Is it my role to remember and list the panels?

Q. If you remember.

A. I seem to recall one.

Q. Do you know the reason why the bioflavonoids were assigned to the panel on hematology and not the panel on obstetrics or gynecology?

A. The reason was not explained to us.

Q. Would you define the bioflavonoids?

What is a bioflavonoid?

A. Yes. The original of bioflavonoids, the original way they were identified as a group to be studied was that it was found in genepicious surveys. At that time, if my [16] memory serves me right, Szent-Gyorgy obtained material that was particularly abundant in citrus fruit, which was thought to be an essential vitamin, then labeled Vitamin P.

Szent-Gyorgy's preparation was shown to contain a group of organic compounds, not one particular material, and I am not enough of a biochemist to go into their structural formulas.

In any event, these were essentially called the bioflavonoids, after doubt arose as to whether they represented a true vitamin.

Q. Are there chemical differences between bioflavonoid products?

A. I don't understand your question.

Q. For example, are there chemical differences between hesperidin and citrus flavonoid compounds?

A. I would think that each extraction procedure—but again, I would not try to qualify as an expert in this area—but, again, each manufacturing procedure would differ, so that each final product would be different.

Q. Do you know whether there are chemical differences between rutin and citrus flavenoid compounds?

A. I would not care to comment on that.

Q. Do you know if there are chemical differences between quercetin and citrus flavenoid compounds?

[17] A. I don't know the definitive answer to that question.

Q. Do you know if there are physical differences between bioflavonoid products?

A. I know that some are soluble in water and some are insoluble.

Q. Are there biological differences between bio-products?

A. This is a question that can't be answered unless biological activity can be established.

Q. Do you know if that can be established in the case of any of the bioflavonoid chemicals?

A. I do not know as a fact if there is any activity on the part of any of the bioflavonoids.

Could I ask you a question at this point, Miss Levine, and that is, if there is any limitation to the area that this discussion can cover?

Q. I think your counsel will advise you about the limitation.

Generally, we are discussing the procedure which you followed as a member of the panel and the discussions that you engaged in.

Mr. HOFFMAN. Incidentally, I wonder if I could ask one question of Mrs. Sisk at this point, [18] and ask—

Mrs. SISK. Are counsel going to take this in tandem?

Mr. HOFFMAN. No. I was going to ask Mrs. Sisk whether you are Dr. Spaet's counsel?

Mrs. SISK. No, we are not.

Mr. HOFFMAN. You are representing only the defendants at this point?

Mrs. SISK. That's correct.

A. To repeat my question, whoever is qualified to answer it, is one of the areas of jurisdiction of this discussion the products of other companies?

Q. To the extent that the bioflavonoids generally relate to

the CVP compound, the specific product involved in this lawsuit, I believe there would be some mention.

A. But you are mentioning them by trade names and not by chemical names.

Q. I have not mentioned any other products by trade names.

A. One of the things that does not come out in a verbal discussion like this, I think when words are capitalized, and I think whenever a capitalized term comes along it should be so designated.

Q. Dr. Spaet, will you state for the record what CVP [19] is?

A. CVP is a proprietary—it is a product of a drug company that contains citrus bioflavenoid compounds, ascorbic acid and a compound known as menadione.

Q. Would you state what CVP without vitamin K consists of?

A. It consists of bioflavenoids and ascorbic acid.

Q. Would you know whether it contains any related phenolic acids?

A. I can only state what the company states is in it, since I have myself done no analytical studies on the product.

Q. Are you familiar with the Freedman-Merritt paper which was a USV study on the flavenoid fragmentation and biological activity of CVP?

A. Not off the top of my head.

The authors, again?

Q. Freedman, F-r-e-e-d-m-a-n Merritt.

A. How was the question put again?

Q. Are you familiar with that paper?

A. The answer is I don't remember having read it.

Q. Would you or do you know whether differences in solubility which you mentioned before, could influence the absorption and, therefore, the biological activity of some [20] of these bioflavenoid compounds?

A. If the question is "could," the answer is yes.

Q. Are you familiar with the paper on the biological activity of the flavenoid compound by Menkin?

A. Yes, I am.

Q. Would you not regard that as a demonstration of biological activity of the flavenoid compound?

A. To the best of my knowledge, the findings of Menkin have not been repeated by other investigators.



Q. Would you regard his paper as demonstrating that?

A. The only thing I can say with respect to that is that he made such a claim in his paper.

Q. Was it demonstrated to your satisfaction in that paper?

A. No.

Q. Why not?

A. Why not?

Q. Yes.

A. Well, by the same token that originally some of the Szent-Cyorgy original observations were later retracted.

It is frequently the case that a single paper will be published and for whatever reason, and the reasons may be many, the work cannot be repeated. Unless there is a body of literature which seems to represent a consensus [21] of opinion among qualified investigators of this type, it does not become an accepted thing in medical literature.

Q. Except for that paper itself, would you have any reason to doubt the validity of it?

A. If I had read it for the first time as a first paper, I would be inclined to go along with it, but in retrospect, since years have passed without confirmatory words, the paper, I think, takes on less significance.

Q. Dr. Spaet, in connection with the panel's review of the CVP products, would you state which products specifically were reviewed? Would you name them?

A. I certainly couldn't do that without the complete list.

Q. If I gave you the list perhaps you might indicate whether or not you recall that the review covered them.

A. It would be only, you know—it certainly wouldn't be something that I would be willing to testify to, but I presume it is a matter of record, is it not?

Q. Do you recall reviewing CVP capsules?

A. As separate from CVP syrup and CVP with vitamin K?

Q. Yes.

A. Yes.

Q. CVP with syrup?

A. Yes.

[22] Q. CVP with vitamin K syrup?

A. Yes.

Q. Duo-CVP capsules?



A. If it is on the list there the answer is yes. But it seems to me there are three items on the list, and I don't recall any product from the USV, other than the ones listed in NDA-9965.

Q. So you are not certain whether or not the panel reviewed duo-CVP capsules?

A. If duo-CVP capsules are not listed here, then I certainly am not certain we examined them.

Q. Bivam?

A. It is not familiar to me.

Q. Prednis-CVP?

A. I am not thoroughly familiar with that.

Q. Prednyl, are you familiar with that one?

A. No. Did we, in fact, review them?

Q. I am afraid I have to ask you that question.

A. Because I have no recollection of any product of these names, and some of them are sufficiently striking so that I would be surprised if I had encountered them and did not remember.

Q. Dr. Spaet, would you state how the Panel on Hematology was organized and what your role in it was?

[23] A. How it was organized?

Q. Yes.

A. I cannot testify as to how it was organized. I can only apply myself as to how the picture of it came to me.

I received—I don't remember whether it was a telephone call or a letter from, I believe—and, again, I wouldn't be certain of this—Dr. Trexler's office, asking if I would be willing to serve on such a panel, and the general mission of that panel was designated in this letter.

When I agreed to do so, I received a formal invitation to do it, and I attended the first meeting with the other members of the panel and the chairman, Dr. Crosby.

Q. What is Dr. Crosby's full name?

A. William Crosby.

Q. When was the first meeting of the panel, if you remember?

A. I don't remember. About three years ago.

Q. 1966?

A. Something like that.

Q. What was your role so far as the CVP products were concerned, in terms of the panel's work?

A. I was given this group of products as the primary reviewer.

[24] Q. You were given it by whom?

A. I am not certain as to who made the assignments. I think it was probably Dr. Crosby who decided who was to be the primary reviewer and who was to be the secondary reviewer, with each group of drugs that we considered.

Q. Was that appointment, so-called, done through a letter or the first meeting of the panel?

A. We each received a package of this sort of documents (indicating), about six inches high, in which a rubber band was around those that were assigned to us.

Q. Would you define what it means to be a primary reviewer?

A. Yes. The primary reviewer was the one who was expected to make the most critical survey of the clinical literature on the drug in question and then draw up a preliminary statement as to how this should be considered by the total committee.

There was also a secondary reviewer who was expected to make up a similar document.

Q. Who was the secondary reviewer on the CVP products?

A. I don't recall.

Q. What kind of document did you make up on your initial review?

A. It was a summary of the literature on the subject, [25] including the principles expressed in certain critical reviews on it, plus a recommendation as to the various categories of evaluation that were given to us to include in our final recommendation and references.

Q. Did you do that by yourself?

A. I don't understand your question.

Q. Did you undertake this primary review alone?

A. I don't understand the thrust of the question.

Q. Did you consult any other member of the panel before you submitted your first report?

A. No.

Q. Did you consult anyone else?

A. No.

Q. In short, you yourself reviewed the literature and called up with the recommendations?

A. That's right. And, of course, the secondary reviewer did the same.

Are you interested in knowing what the sequence of events were next?

Q. I would be.

A. All right. The statements that we made were then sent around to all members of the panel for comments, and then the comments were collated at a meeting that we had and which we all attended.

[26] So that the first aspect of it was done by mail, so that the other members of the panel would be prepared, and when they came—when the time came for discussion they would not be receiving any information cold, they would have an opportunity to check on some of the references if they wished and to add additional material from their own specialty or additional references if they might have wished to comment.

Then the panel then met and discussed any point of difference, and then a tentative second draft of the document was drawn up, which was again sent around to the entire panel for additional comments, and it was finalized sometimes at the next meeting or sometimes it took a couple of meetings.

Q. Dr. Spaet, could you confine your testimony to the CVP products specifically?

A. I don't remember specifically how they applied to the CVP products. I would be certainly willing to state that in addition to the remarks we made—the primary and secondary reviewer made—there were additional remarks made by other members of the panel, which I do not recall.

For example, one member of the panel referred to us a paper in which it was felt that some of the biological activity attributable to these was due to unsuspected [27] action of ascorbic acids.

Q. Dr. Spaet, specifically what did you evaluate in connection with your first review? Did you evaluate the materials submitted by the company?

A. Yes, we did.

Q. Did you evaluate the FDA file?

A. Yes, we did.

Q. Do you recall what material it was that was submitted by the company to you?

A. Yes, the company submitted essentially three things:

The photostat of the label, a photostat of the package insert, if I am not mistaken, and also a card that contained some additional material; and in addition to that, the company submitted a list of references.

Q. Biographical references?

A. Yes.

Q. What was the card?

A. The card contained indications other than those mentioned on the package itself.

Q. Was that a physician's file card?

A. Yes.

Q. Did you, in your consideration, look at any other material than that submitted by the company?

A. Yes, we did.

[28] Q. Would you state what that was?

A. Yes. We did a literature survey and read papers that were—that were other than those favorable to the product.

Q. When you say "we," Dr. Spaet, to whom are you referring?

A. The primary and secondary reviewer, and I presume other members of the panel.

Q. You are the primary reviewer?

A. I was, yes. Sometimes I am going to use the term "we" in the royal sense, so catch me up on it.

Q. Dr. Spaet, would you recall whether Dr. Frank Gardner was the secondary reviewer?

A. I would not recall specifically whether Dr. Frank Gardner was the secondary reviewer.

I would say that Dr. Frank Gardner is also active in the field of investigation of hemorrhagic disorders.

Q. If I were to read to you the other members of the panel, would you indicate whether any of the others were the secondary reviewer?

A. I can't make a statement.

Q. Do you recall whether Dr. Hugeley was?

A. No.

Q. Dr. Schilling?

[29] A. No.

Q. Dr. Zuelzer?

A. I do not.

Q. Dr. Spaet, you stated that you submitted to the panel after your review a statement or an evaluation; is that correct?

A. Yes.

Q. Can you tell us what the nature of that statement was?

A. I am repeating what I previously had said, if I am not mistaken, and I hope it corresponds fairly close to it. It consisted of the following:

A summary of the published findings of papers reporting results with these drugs, plus a summary of the conclusions we

reached by people who had reviewed the subject, plus an evaluation, according to the ground rules laid down on my own part, as to where I figured this group of drugs should be classified.

Q. And that was submitted to each member of the panel?

A. Yes.

Q. Where would that statement be at this time?

A. I have no idea.

Q. Did you keep a copy of it?

A. No, I did not.

[30] Q. Did you receive a copy of a report from the secondary reviewer, whoever he may be?

A. I did.

Q. Do you have a copy of that?

A. I do not.

Q. Do you recall whether his conclusions as evaluations were the same as yours?

A. They were.

Q. Did you ever refer the question of the effectiveness of CVP products to another panel?

A. I don't recall.

Q. To an outside consultant?

A. To an outside consultant, we did not.

Q. Incidentally, Dr. Spaet, did you or the panel——

You had no question, did you, about the safety of the product?

A. I would like you to clarify your question.

Q. Did you have any question whatever about the safety of these products when taken orally for the conditions represented?

A. You are raising, again, an extremely complex question and a yes or no answer would certainly not suffice.

Let me clarify my own feelings and, I think, the feelings of the panel, and if I am not mistaken, also the [31] guidelines laid down with respect to safety, as we understand them in terms of how the panel interpreted them.

If an individual has a disease that requires therapy and this therapy is delivered by administration of an inefficacious product, which is thought by physicians to be efficacious, from our point of view it meant that the agent was not safe.

If you are giving, for example, a placebo to treat a severe infection, even though this placebo in itself might not damage the patient, it was not safe.

Q. So as far as the safety or toxicity of these products per

A. I think there is a difference between safety and toxicity in this sense: You might say there is a category of reaction called pharmacological toxicity, in which an individual, a normal individual, given these agents would not develop adverse reactions.

In this sense, we did not consider that the bioflavonoids had that type of pharmacological toxicity.

On the other hand, if a patient had a bleeding disorder and a physician who was influenced by material on the subject gave it in place of definitive therapy, this would be unsafe.

Q. What definitive therapy would be recommended in [32] place of CVP?

A. For what condition?

Q. For abnormal menstrual bleeding?

A. Abnormal menstrual bleeding can occur on the basis of several different etiologies.

It is, for example, thought in 1969 that one source of abnormal menstrual bleeding is the administration of aspirin.

Removal of the aspirin would be the treatment in that case. This is an example.

There are many other possible causes of abnormal menstrual bleeding. For example, a woman will have abnormal menstrual bleeding if her blood platelet count is very low.

One example of appropriate treatment for that would be removal of the spleen.

Q. Dr. Spaet, in your consideration of these products, did you take into account their wide acceptance by many doctors and their accepted usage over the years? Was that a factor in your evaluation of these products?

A. It was not.

Q. It was not?

A. No.

Q. Would you explain why?

A. Yes. We feel that many inefficacious products are widely accepted.

[33] Miss LEVINE: May I suggest we take a five-minute break.

(Short recess taken.)

Miss LEVINE. On the record.

The WITNESS. I would like to say I was asked somewhere along the line whether we considered the original FDA file in reviewing this drug, and I answered yes to that. That is erroneous.

We had not gone over the original FDA file.

By Miss LEVINE:

Q. You reviewed only the Form A submission of the company?

A. Yes.

Q. And the literature that was cited there?

A. Not only the literature that was cited there; the literature that was cited and in addition, the literature we ourselves uncovered.

Q. Dr. Spaet, you stated that the literature which was cited by USV was unsatisfactory, I believe?

A. I did not say unsatisfactory, I said incomplete. I didn't say that, I implied it.

Q. Would you state why it was incomplete and what other literature you consulted in connection with your evaluation?

[34] A. The reason it was incomplete, of course, was that it only contained material favorable to the product.

Q. Aside from the fact it was favorable, what were the defects in it?

A. The defects in the papers cited by the Company were that they were unconvincing for the papers made for the efficacy of the drug. In addition to that were papers we obtained from various sources, but that they included negative studies and evaluations from other physicians who had done complete reviews of the world's literature on the subject.

Q. Why were the papers unconvincing?

A. I think this raises a question as to what it takes to create a convincing paper.

On the basis of criteria that I think most investigators would accept—first of all, the possibility of bias in any study has to be eliminated, and the way this is eliminated is to do essentially two maneuvers: First of all, one has to have a group of patients who are being treated with the presumably effective agent and a control group that is being identically treated, but just missing the active ingredient present in the others.

Secondly, neither the patient nor physician nor anyone else involved in evaluating the effect should be aware [35] of what is being given.



In other words, the general principal of a double-blind study. The patients should be randomized in such a way that there is no bias with respect as to who falls into which group, and none of the papers cited were anywhere close to that type of study.

Q. Were any of the other papers that you consulted based on that kind of study?

A. The closest to it was a paper published in 1944, that I have in my file here. This one (handing), by Rudy, Beaser and Seligman, and a group of papers—they were not done double-blind, but groups of controlled patients, with respect to the effectiveness of bioflavonoids in increased capillary fragility of diabetes mellitus.

Q. Do you know what specific product was used in that test?

A. Hesperidin, and the trade name of the product was Eriodictyol.

Q. What is Eriodictyol.

A. It is a proprietary preparation of bioflavonoids, available in 1944. I don't know if it still is available.

Q. But this test was done with hesperidin?

A. Yes.

[36] Q. And this was before CVP was in existence?

A. Yes.

Q. Were any of the other papers you consulted based on the kind of study you think is essential?

A. No, these studies seem to be unavailable with respect to a preparation of this sort.

Q. So the only studies you find which were satisfactory, was the Rudy, Beaser & Seligman study in 1944?

A. I don't recall any other studies—wait a minute. I would have to go back to my original files.

If memory serves, there were a couple of other double blind studies that were performed with negative results.

Q. Were any of them performed on CVP?

A. As far as I know, no, but I would not be sure of that.

I would like to add that any preparation containing ascorbic acid could have effects attributable to the ascorbic acids.

Q. Dr. Spaet, if you could look at your files and see whether any of those other studies were appropriate ones in your view, we would appreciate having that supplied to us.

A. Fair enough.

Would you again includes this in the letter you send me?



A. Yes.

[37] A. In reply to that, do you wish me to confine myself to CVP or any other bioflavenoid preparation?

Q. To the extent that your comment on CVP would take into consideration other bioflavenoid products, I think it would be relevant.

A. All right.

Q. Dr. Spaet, I show you the document under Log. No. 734, which you brought with you this morning in response to the subpoena, and ask you to look at the last page of this submission entitled "Reference."

Do you know whether the Jacob study was a double blind study of the kind to which you referred before?

A. The Jacob study I don't remember. I did not review that in detail for this session for the following reason:

Our panel was not dealing with the Rh problem, and this was not considered as a problem within the jurisdiction of the assignment given to us, that is, with respect to the bleeding.

Q. Would you define specifically what your assignment was?

A. Our assignment—

Q. In connection with CVP.

A. Yes, with respect to CVP. A problem arises, and [38] that is that we were not assigned the card which is Xeroxed here (handing), or we were not assigned the contents of the PDR Physician's Desk Reference.

Mr. HOFFMAN. Let the record show that Dr. Spaet has referred to a copy of Physician's File Card.

By Miss LEVINE:

Q. Would you specify what your assignment was?

A. Our assignment was only the package insert.

Q. Would you recall what the condition of use was?

A. Yes, it was stated that the package insert was—to the effect that these were supplementary sources of—supplementary vitamin sources or something to that effect.

Q. Do you have a copy of the package insert to which you are referring?

A. It is on there (indicating). The page before that. There it is (indicating).

It reads as a supplementary source of bioflavenoids, ascorbic acids—

Mr. HOFFMAN. Let the record show that the witness is referring to page 3 of the 7-page document which Dr. Spaet

brought with him today in response to the subpoena, designated Log 734 at the top.

Q. Dr. Spaet, when you say a package insert, are you or do you mean to refer to this written material on this [39] page?

A. I do.

Q. Did you not review any other material in addition to this page, in connection with CVP?

A. We did not. In connection with CVP, the answer is, we did not.

Q. Are you aware that that page incorporates three label statements from CVP?

A. I am.

Q. And that that is not the package insert?

A. What was given to the panel to review was done by the administrative components of the panel.

In other words, we were handed material, and from this we were to ascertain what the claims were.

Q. Dr. Spaet, would you, for the record, state what is contained as a condition of use for each of the products on that page, identifying the products?

A. Yes. CVP with vitamin K tablets.

It was advised that caution be used on the treatment of pregnant women.

Q. The condition of use. What was it recommended for?

A. As a supplement source of bioflavenoids, ascorbic acids and menadione, and the same applies to CVP with vitamin K tablets, capsules and syrup.

[40] Q. So I understand you to say that you did not review the package insert for this product which contained conditions of use under a prescription legend, but only the conditions listed on the labels which you have just read?

A. That is correct.

Q. Then there was no consideration of the CVP products in capillary fragility?

A. These specific products, no, but in other companies, preparations of bioflavenoids, there was.

Q. What was the reason you did not consider the package insert or the Physician's File Card which is listed in that document, Log No. 734?

A. Because the source of indications as presented to the panel lists was provided by the administrative component of the panel, and we only considered what was presented to us.

Q. Would you state what the administrative component of the panel was in this particular case?

A. Yes, there was an executive secretary who screened the material that came to us so that our job would be made easier, so that we wouldn't have to go shuffling through specific labels and package inserts and things of that sort, and he would ferret out of these that which we were to consider.

[41] Q. Would you state which products, which bioflavonoid products you did consider, in terms of conditions of use in bleeding disorders and the like?

The WITNESS. I would like to ask Mrs. Sisk if at this stage of the game we are going to discuss other products?

Mrs. SISK. It is all right.

A. Rutin was one, a product of Abbott Laboratories. Ruterbin, a product of Squibb.

Q. Dr. Spaet, as you are referring to these would you designate the long number?

A. 798 in the case of Rutin, 1997 in the case of Rutorbin, and 2407 in the case of Rutin made by Parke-Davis.

1504 in the case of quercetin of Abbott Laboratories.

Q. Then your evaluation, again, Dr. Spaet, was confined to CVP as a supplementary source of bioflavonoids?

A. That's correct.

Q. And you did not give any consideration to the effectiveness of CVP in capillary bleeding?

A. Not in the evaluation we submitted.

Q. In habitual or threatened bleeding?

A. Yes.

Q. And normal menstrual bleeding?

A. That's correct.

[42] Q. Gingival bleeding, non-thrombocytopenic or in strengthening the placental capillary barrier against escape of fetal red blood cells into the maternal circulation?

A. That's correct.

Q. Dr. Spaet, we will go back for a minute to the question of biological activity.

A. Yes, ma'am.

Q. Do you know whether there is pharmacologic evidence of the specific activity of the citrus flavonoid compound which is incorporated in CVP?

A. I pass.

Q. What would your answer be, Dr. Spaet?

A. My answer would be I am not aware of specific evidence—of the specific convincing evidence of pharmacological—well, pharmacological activity has been claimed for the citrus bioflavonoid compound found in this preparation.

I am not prepared to evaluate it at this point.

Q. Are you familiar with Lung Proteolysis, published by Ungar?

Miss LEVINE. Off the record.

(Discussion off the record.)

A. Then I am not familiar with the particular studies.

Q. Are you familiar with the anti-genic serum test?

[43] A. I am not.

Q. Are you familiar with other anti-inflammatory test procedures which are believed to involve capillary or collecting venules?

A. I am familiar with such a test, however, I am not familiar with how they have been applied to this particular group of compounds.

Q. Do you know whether the citrus flavonoid compound which is incorporated into CVP is active in all of these tests?

A. I do not. I would like to, however, add that our assignment was not to ascertain whether or not biological activity could be demonstrated in animals, but whether these agents had chemical efficacy.

I will state we did not review the animal literature with the same kind of diligence that we reviewed the human disease literature, and there are, of course, many reasons for this.

Our assignment was clinical efficiency. We were not concerned with what drugs the rats might purchase.

Q. Dr. Spaet, did you ever see the supplemental submission which the USV Company made to the FDA, dated February 15, 1968?

A. I did not. To my memory, I did not.

[44] Q. Do you know whether any member of the panel ever saw that submission?

A. I do not know.

Q. Did you ever see the paper written by Dr. E. M. Clayton, entitled "Effective Citrus Bioflavonoid Carbazochrome Salicylate and Ascorbic Acids on the Transplacental Passage of Fetal Erythrocytes," which was published in 1967, in the journal of Obstetrics and Gynecology?

A. No. I would like to add, however, that this particular reaction would not have come under the jurisdiction of our scope in any case, because our assignment was with respect to bleeding and the transplacental passage of cells is on the basis which has not been fully established. I am not sure that this entire subject would have been appropriate for the Hematological Panel.

Q. What panel would it be appropriate for?

A. I suspect the Obstetrical Panel, but that is just a suspicion.

Q. Did you ever see the report by Dr. Milton Gotlib, entitled "Clinical Evaluation of the Role of Duo-CVP in Menometrorrhagin Associated with I.U.C.D."?

A. I don't recall that publication.

Q. So that neither of these papers was taken into account in the panel's evaluation of CVP?

[45] A. I don't recall that they were.

Q. And neither was taken into account in the evaluation of any of the other bioflavonoid products?

A. Well, they wouldn't have been appropriate for other bioflavonoid products, since this contains ascorbic acids, and the pharmacological activity of flavonoids would have had to have been separated out, under separate circumstances.

Q. Would the review of that paper, from the title, have been appropriate for the panel on hematology?

A. I think not. Menometrorrhagia is sometimes, but usually not a hematologic disorder.

Q. Was there something else you wanted to add?

A. Me?

Q. Yes.

A. No.

Q. You said it would have more appropriately been referred to another panel?

A. The referral to other panels was not my decision.

I think it probably was a mistake I made a suggestion of referring a drug to another panel previously, and I think that my remarks should be stricken from the record.

Q. We will take your comment into account, but we won't strike it.

[46] A. Okay.

Q. Are you familiar with Clemetsen's work on the presence of the oxydation of ascorbic bioflavonoids in humans?

A. I have heard of the work, but I am not familiar with it.

Q. I gather this paper was not taken into account in your evaluation?

A. Well, it was taken into account in the sense that we considered the possibility that this might be a useful action of the drug, but did not feel it was adequate for the claims made for it.

Q. Which claim are you referring to?

A. The claim that it has a separate effect of ascorbic acids on blood vessel integrity. I am not talking about CVP, I am talking about bioflavonoid integrity.

If the blood prolongs the action of ascorbic acid, then the presence of adequate amounts of ascorbic acids would not be improved upon.

Q. Dr. Spaet, in the report on CVP which was submitted by the panel, the citation which appears on the bottom of that document is to Byrnes.

Was the Byrnes evaluation based on the kind of double blind clinical study to which you previously referred?

[47] A. No, it was not. The Byrnes evaluation was a section in the chapter of the standard textbook of pharmacology, Goodman & Gilman, which is the Bible in its field.

What Byrnes has done in this case is something similar to what the panel did, that is, evaluate the literature and came to a conclusion.

Byrnes was not used as the source of information, but was used as a statement from an authoritative individual that agreed with our own, I would say for sake of economy, for citation.

There has been earlier papers in which the establishment of the bioflavonoids as a vitamin had been discounted.

Q. Do you recall whether the Byrnes review of the bioflavonoids as a vitamin had been discounted.

Q. Do you recall whether the Byrnes review of the bioflavonoids referred specifically to studies using CVP?

A. I don't recall that it did.

Q. So that Byrnes' comments were based on studies involving rutin or hesperidin, other bioflavonoids?

A. Yes.

Q. Other bioflavonoids than CVP?

A. I don't know without referring back to Byrnes.



Q. Would this be true also of the comment by Yaoming, which is the other study to which the panel referred?

A. I think it would.

Q. To what extent was the evaluation of "ineffective" [48] based on—had it been the informed judgment of the panel?

A. How do you quantitate that?

Q. I believe this is a criterion that was mentioned in the NASNRC report itself.

A. Well, I think that in the last analysis the evaluation is 100 per cent of informed judgment of the panel. The conclusion derived by the panel from all of the evidence presented to them. The panel has not in any of these cases, except coincidentally, done original research in the areas under discussion, so that what they are doing is evaluating the literature and adding to it their own background in the field.

Q. Dr. Spaet, in the case of CVP, would you state for the record the exact nature of the—the exact procedure that was followed by you in making the evaluation and referring it to the panel? You mentioned it generally before, I believe.

A. Yes. I don't recall the exact procedure in the case of the CVP.

I would not be able to dissect out of the various bioflavonoid preparations the exact procedure for each separate one.

Q. You evaluate all of the products together, all of the bioflavonoid products?

[49] A. In going through the literature, this is obviously what had to be done.

In evaluating the specific claims made by each product, this was done individually, based upon the wordings of the claims, which were different in each case.

Q. Was that done by you?

A. It was done to a certain extent by me and to a certain extent with the collaboration of the panel.

In other words, the panel would sit down and say to each other, there is a difference between this claim and that, although it sounds similar, for example. But the details of how it applied to CVP are lost to my memory.

Q. You made an evaluation incorporated in a document which was circulated to all members in a panel, which was before a panel meeting?

A. Specifically with CVP?

Q. Yes.

A. I don't recall that was the case.

Q. Generally with the bioflavenoids?

A. Yes, generally with bioflavenoids. Specifically with CVP, I don't recall that.

Q. Do you recall at which panel meetings CVP was used?

A. No, I cannot.

Q. Do you recall any panel meetings that were devoted [50] to a discussion of CVP or the bioflavenoids?

A. I do not.

Q. How was the report which appeared on page 5 of the 7-page submission under Log No. 734, how was that report compiled and drafted?

A. Well, again a preliminary copy of this, as applied to claims, was written up by—specifically whom, I don't know. In the first case, I don't recall whether I did or Dr. Middleman did. And this was then circulated to all panel members for comment, and then at a meeting of the panel the pile of the drawings that we were considering at that particular meeting was set in front of us, and we went through them one at a time for any further corrections or comments.

A final copy was compiled, and based on that it was sent to the panel for approval, and if there was no comment, it went to the FDA.

Q. This was generally on bioflavenoids?

A. This applies specifically to CVP. That is, every member of the panel saw every report of the sort you are seeing here and had the opportunity to comment as he saw fit.

Miss LEVINE. Off the record.

(Discussion off the record.)

(Whereupon, at 12:05 p.m. a luncheon recess was taken.)

[51]

AFTERNOON SESSION 1:20 P.M.

[Theodore H. Spaet, the witness, resumed and testified further as follows:]

Examination (Continued) by Miss LEVINE:

Q. Dr. Spaet, you testified, I believe, that the panel had evaluated CVP with respect to its usefulness as a supplementary source to bioflavenoids only?

A. Yes.



Q. What was the reason that you were consulting the literature relating to capillary fragility which had been supplied by the Company on Form A?

A. Well, this was a source of reference that was useful to some of the other agents, and there was, of course, some overlap. But when the final evaluation came out on CVP, we did not know that this was going to be the single consideration.

When we got bioflavonoid preparations, we assumed that in general, since they are used for bleeding disorders, that they would all include that, so that in the process of searching the literature I used what I anticipated would probably come up.

Q. Is it valid to equate all bioflavonoids with respect to efficacy for all conditions of use that are repre [52] stated in the labeling?

A. Probably not.

Q. Would you explain that?

A. Well, if there were a single compound involved, such as, for example, aspirin, as an identified chemical compound, then a statement that applied to one preparation of it could apply to all in equal manner and equal degree.

On the other hand, when you are dealing with a group of compounds with undetermined differences in the method of extraction, and undetermined differences between the ratio of one and the other, and perhaps a single member of the group, under the circumstances then a statement cannot be universally applied as they could be with a single compound.

This is a hypothetical question, of course, because if there were a question of efficacy in one, and one tried to bring it to the other, under the circumstances it would arise as to whether they were the same compounds. If no one of the group contained an efficacious material, it wouldn't matter what the variation might be from one to the other.

I would give an example in this case of, say, mineral water in the treatment of bleeding disorders.

Mineral water has various compositions, but if there [53] is no evidence that any one mineral water works, one needn't be preoccupied with the differences between them.

Q. Would you apply the findings on efficacy that were made as to rutin to CVP?

A. Well, the problem in this case is that rutin is a preparation containing bioflavonoids only. CVP contains ascorbic acids. Obviously the ascorbic acid is going to have reactions not mani-

tested by rutin, so the statement could not be used interchangeably.

Q. Would you apply the findings on rutin to the citrus flavonoid compounds of CVP?

A. Well, I would apply the findings by any publications supporting efficacy of a product only to that material if there were efficacy.

In the absence of efficacy, then there is no evidence that the drug is efficacious and there is nothing to apply.

Q. In this case, Dr. Spaet, there were findings as to the lack of efficacy of rutin for any condition.

A. Excuse me. It was the lack of findings for efficacy, not the lack of efficacy that we are concerned with.

In other words, there is no study that demonstrated beyond a reasonable doubt that these agents are inefficacious. As I mentioned earlier, our guidelines were that [54] the burden of proof rested on the company supplying the copy. It rested on them to demonstrate that their product was efficacious, and in none of these cases was there any such a demonstration, in any form, in any combination, with respect to the bioflavonoids or with respect to any other possible member of the group.

Q. But the failure of the copy which you found to make a showing of efficacy of rutin, could that be applicable to CVP?

A. No, it could not. CVP has its own failure to show efficacy.

Q. For what use did you find, doctor?

A. Well, the use that we applied ourselves to in this particular report is the only one I can make a statement about, and as we stated, since there is no established requirement for the components of this drug, then its inclusion did not demonstrate efficacy.

Q. In discussing Menkin's paper, you referred to the need for a consensus of qualified investigators, if a finding is to be accepted as part of scientific knowledge.

A. Yes, it is to be incorporated into the body of scientific knowledge, right.

Q. Is that the standard you used in reviewing CVP?

A. We are dealing with two different subjects. [55] Menkin's studies were animal work.

In CVP, we are concerned basically with the efficacy of this study, whether Menkin's work would be applicable would be a completely different question—

Q. I think you misunderstood the question. It was a question as to whether or not the standard you applied in reviewing the product was that of the consensus of qualified investigators.

A. Let me rephrase the question and see if this is what you intend, before I answer.

Q. I would be delighted.

A. Do you mean if I were to head a group of hematologists, whose particular excellence was the bleeding disorders, that they would accept the kind of studies that are published in support of CVP?

If that is not your question, then I don't understand your question whatsoever.

Q. You are not reviewing CVP with respect to bleeding disorders.

A. That's right, but you asked me a hypothetical question.

Q. I asked you what standards you applied.

A. In this particular case, the standards we applied were, did the package insert have a statement which efficacy [56] would correspond to it.

And the prevailing opinion at that time, in 1965, was that there is no established vitamin P. The body of expert opinion on this is that there is no vitamin P. Accordingly, the use of vitamin P as a vitamin would not be an efficacious step.

Q. Was the standard the body of expert opinion?

A. The standard in this particular case was the conclusion as determined by two components: one was a withdrawal of the original concept as enunciated in the first place by Szent-Gyorgy. He went back on his concept that vitamin P was a vitamin.

Number two, that the authoritative documents, such as Goodman and Gilman in 1959 and '66, did not consider P to be a vitamin.

These are the two types of opinions on the subject.

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

Miss LEVINE. On the record.

By Miss LEVINE:

Q. In coming to the conclusion that CVP products were ineffective, what were the standards or the criterion that you applied in reaching that conclusion?

A. I think the answer to that question, as I see it, [57] breaks down into two parts.

The first is the general principle that if a component of a preparation is inefficacious, then the use of that component in a mixture is an inefficacious step.

The next question that comes up is why this component is inefficacious itself as a vitamin supplement.

Q. What I am asking you is whether or not you based your conclusion on a consensus of qualified investigators or the lack of a consensus of qualified investigators.

A. Oh, well, the—it would be the lack of consensus, I would say, for this reason: that there was not a group of qualified investigators who did the studies, that demonstrated that so-called vitamin P was not a vitamin.

There was no body of evidence collected into one review in which many negative studies were collected. It is the lack of confirmatory evidence that a deficiency state existed as to this group of material, which could be corrected in the way a classical vitamin deficiency is corrected.

There was no further body of confirmatory evidence along with reversal of the convictions of some of the investigators who originally held these opinions.

Now, again I think we are probably tied up a little bit on the problem as to what constitutes a body, now [58] many members have to be present to constitute a body.

I know a minion, but a body is not clear to me.

Q. Dr. Spaet, under the standard which you applied, if there was a substantial amount of well-documented favorable evidence, but if some of the evidence were not conclusive, would that preclude a finding of effectiveness?

A. If there were a body of favorable evidence, of course we would have a different viewpoint, a body of favorable evidence that fulfilled the criteria I outlined earlier. Of course the presence of bad studies does not mean good studies could not come along.

I think the same situation prevails here as prevails with flying saucers, that there is a large body of evidence that has been presented, and the people who have considered flying saucers say if we see a good study on the flying saucer we will accept it.

Q. We are in a little different realm here with CVP.

A. Explain that to me.

Q. During any of the panel meetings, did any panel members express the opinion that CVP should be placed in the possibly-

effective category rather than in the ineffective or any condition category?

A. Never.

Q. Any biflavonoid product?

[59] A. Never.

Q. You mentioned that the Beaser study in 1944 was one of the literature references which you considered unfavorable to the bioflavonoids generally, though it did not specifically deal with CVP?

A. Yes.

Q. Would you list the other unfavorable literature references on which you relied for your evaluation of CVP?

A. Well, I would have to give you one or two off the top of my head.

In Quick's Textbook of Hemorrhagic Disorders he mentioned that some investigators have used this in the treatment of hereditary hemorrhagic telangiectasia. Quick mentioned that he had no satisfactory results in attempting to duplicate these findings.

Q. Was this a controlled study?

A. No, he just states—this is one that sticks out in my mind.

Controlled studies of this sort, as I mentioned earlier I do not have with me but I will, if I can dig them up, send them in in a letter I am apparently going to send to you.

Q. Have you completed the literature references that you were thinking of?

[60] A. Yes. I thought rather than talk off the top of my head I should get back to more solid evidence.

Q. Were any of the unfavorable references cited in the panel's report?

A. The panel's report cited only summary papers.

Q. It did not cite any of the—

A. It did not cite the original work, that's right. It cited, as you know, the paper by Byrnes and the one by Yaomins, and I could not know if some of the other products there were additional references specifically cited, but it was felt that these would give a summary opinion rather than go back to specific individual papers, that this would be sufficient for the purposes of presenting our viewpoint.

Q. When you say it was felt, by whom was it felt?

A. By the panel.

Q. By Dr. Crosby?

A. No, the panel. All decisions that were made were group decisions.

Q. Was that placed on your recommendation?

A. As to which references should be used?

Q. Yes.

A. I don't remember how that specific designation came up. I don't remember also whether there were any [61] guidelines given to us as to how extensive our citation of the literature should be in documenting the decision.

I don't know that the guidelines were specific about that.

Q. If there were substantial pharmacologic evidence of biological activity of citrus flavenoid compounds and you were aware of it, would the clinical evidence be reviewed in a different light?

A. You mean if there were convincing evidence that the bioflavonoids—I am trying to rephrase your question so that it is clear to me.

If there were convincing evidence that the bioflavonoids had an antihemorrhagic effect in animals, would we have looked at the data differently; was that your question?

Q. Specifically with respect to CVP.

To clarify it, its pharmacological activity which would underlie the effect on bleeding disorders.

A. Well, what I do wish could happen is that Dr. Sadow and I would do this directly, because this would clearly cut through a lot of ice. Is it possible—

Q. No. I think the question should be answered.

Dr. SADOW. You and I will have to sit down one day and talk separately.

A. The question, if I understand it, if there were [62] some convincing evidence that there might be some possible relationship between this and blood vessel function in animals, would I have taken a different view to the clinical studies that we looked at; is that right?

Q. I was talking about the citrus flavonoids compounds.

A. Now there has been—I will maybe try to help you a little.

There has been some claim made in the literature that citrus bioflavonoid compounds have an effect on maintaining the material ground substantial. Ground substantial is a non-specific term.

I think most people working in the field would prefer to use the term mucopolysachrites.



The question you are trying to ask me is if it could be conclusively demonstrated that mucopolysachrite integrity would somehow be influenced favorably by administration of bio-flavenoids, would this alter my viewpoint with respect to the clinical study.

Q. I don't think that was the question.

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

[63] A. No matter what animal studies show, if clinical studies are unsuitable, then efficacy is not demonstrated and no animal orientation is permitted to help.

Did that cut the knot?

By Miss LEVINE:

Q. Referring to the literature references attached to Form A, was the Carvel study, Part 2, a double blind study?

A. The Carvel study stated as follows:

If I am not mistaken—

Q. Was it a double blind study?

A. My answer, I think, will make this clear. A double blind study was attempted but it—I think this was the one—but it was clear that the physician could tell the differences on the basis of odor or something of that sort which were the placebo or which were the so-called active medication, so that a so-called double blind study was not actually performed.

There is one of the papers in which a double blind study was considered. Is that it (indicating)?

Dr. SADOW. No, that is not the one.

A. [Continuing.] If it is not that one, I would have to review. But the problem with that study was that he specifically states that the patients were suffering from malnutrition, and any correction in this study could have [64] been the correction of scurvy.

Q. Is the Carvel study the one that you brought with you, Doctor?

A. Yes.

Q. Can you establish whether that was a double blind study?

A. The whole study surely wasn't. Seven patients took part in the double blind study.

Let me read from this.

Q. Not at the moment, Dr. Spaet.

Was the Beaser study of 1944 a single blind study with Eriodictyol?

A. Yes, it was.

Q. Do you accept the results of that study?

A. Well, the point in this study is the differences were not shown.

Q. It was a single blind study?

A. Yes, it was.

Q. Was the company study which is cited in that submission a single blind or double blind study?

A. Company?

Q. On functional menorrhagia?

A. I don't know that.

Q. Was the Clemetsen study a single blind study?

[65] A. Yes, it was a single blind.

Q. This related to duo-CVP as against lactus placebo?

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

Mr. HOFFMAN. On the record.

Can you repeat what you just said to me?

The WITNESS. I was informed if the answers that were requested from counsel did not give a clear view of my opinion, that I would be given the opportunity to elaborate on them.

Mr. HOFFMAN. Without getting into, right now, the question of who informed you, we would like to inform you that, if your answer conveyed the sense of the answer to the question that was asked, your answer will stand.

Only if you feel that the answer is not an answer to the question as you would like to state it—

The WITNESS. Are you stating that additional matter cannot be volunteered?

Mr. HOFFMAN. If it is not in response to a particular question, it cannot be.

Mrs. SISK. It can be if it is part of the answer.

The WITNESS. How is it ascertained that it [66] is part of the answer?

Mrs. SISK. If Dr. Spaet wishes to say something in addition to his answer, so his answer will be clear, of course Dr. Spaet may be able to do so.

Mr. HOFFMAN. The question was whether it was a double blind study, and it calls for a yes or no answer.

A. In the case of Carvel, it is true that a double blind study was done, but the double blind study did not relate in any way to bioflavonoids.



The patients were stated specifically as suffering from debilitating diseases.

I don't think anyone in the FDA or out of it is going to argue that ascorbic acids can improve persons with scurvy.

Also, it might be added that a double blind study in itself is not adequate to establish an observation.

A double blind study has to be done with adequate controlled patient selection and adequate evaluation of the data.

I think that in this study that clearly what Carvel and associates are dealing with is vitamin C deficiency.

Q. You are not excluding single blind studies as being acceptable?

[67] A. They may be acceptable, but I think that each single blind study has to be evaluated in its own right.

Q. Getting back to Clemetsen's study, did it employ an objective test procedure as a further measure of clinical response?

A. The answer as to the objectivity of capillary fragility studies is not as clear cut as Clemetsen would have you believe.

I refer you to the statement made by—

The WITNESS. May I have that file over there?

Mr. HOFFMAN. Yes (handing).

A. [Continuing.] Somebody did some studies, and I believe it is back to our old friend again in the archives in 1944. I believe it is a completely satisfactory method, even in 1966, if the—

Q. Do you know the method?

A. Yes. They used a negative pressure method. There were many problems with it.

Q. Doctor, how can you do a double blind study on threatened abortion?

A. Well, if you would like me to set up a study, I would be glad to do it for you.

Q. Would you describe—

A. In general how one might do it?

[68] Q. Yes.

A. Yes. What one would do is to randomly select women who are pregnant. That is, you take all women who are pregnant who show the following sign: A certain age of pregnancy. And then in a group of cards that are shuffled up, completely at random fashion, assign them to Group A or Group B.

The women you select would not be all pregnant women, but ones who have certain criteria for threatened abortion, which

I could apply myself to superefficiency, but I would have a group of gynecologists and obstetricians lay down as to which patients should be selected from this group.

These women are completely randomized, so that no bias can creep in.

Then what you would do, according to their cards, give them either a compound you are testing or a placebo that differs from the compound you are testing only in the absence of the ingredient you are testing. The personal administration of the material, the person taking it, the person evaluating results should not know which group the patient is in, and then whether those women go on to a full pregnancy or not should be ascertained by techniques used by people qualified in the field.

The data should be collected until such time as a [69] sufficiently large sample is established to ascertain the significance of it, and it should be written up and reported in a suitable medical publication.

Q. But there would be a risk that the woman on the placebo would abort?

A. There would be a risk that the women on active ingredients would abort, of course, and the reason you are doing this double blind study is because you want to know the answer.

There are double blind studies being done all the time.

Q. Would obstetricians generally want to take a study of this kind?

A. They would generally not, because they are busy, they are not scientists—we have had all kinds of pressure put on us when we have had studies of this sort—you read Arrow-smith.

Do you remember how it turned out when the wife got sick? She was not randomized.

So it is simply difficult to set up such studies.

The WITNESS. Off the record?

Miss LEVINE. Off the record.

(Discussion off the record.)

A. [Continuing.] I don't think that it is impossible to set up such a study.

[70] I should like to add for the record, that the study of Clemetsen that we have just been discussing, also is one in which the possible effect of those being tested is ascorbic acid.

Miss Levine, how can you possibly go for a point to prove—I am trying to show you the difficulty you are confronted with. This is a preparation of vitamin C.

Q. When was the report, the panel report, finally approved on CVP?

A. The date I don't remember.

Q. Do you know approximately?

A. About a year and a half ago, I should think. But it is not an authoritative statement at all.

Q. Was this about the fall of 1967?

A. That would seem like a reasonable time.

I seem to remember having a January deadline in my mind, but I don't remember which January it was.

Q. Would it have been January of '68?

A. That sounds reasonable, yes.

Mr. HOFFMAN. Dr. Spaet, we have just a few more questions on a general subject which I propose to put to you, then I think you will be ready for cross-examination.

[71] By Mr. HOFFMAN:

Q. Did you ever, prior to the filing of your final report on CVP and on the other bioflavonoids, discuss the work of the panel or your proposed report with any official of the Food and Drug Administration?

A. You mean aside from members of the panel and the executive secretary?

Q. Yes.

A. No. All of the discussion that went on was through the chairman. In other words, we never spoke directly to other officials.

Q. Did you have any communications with the Food and Drug Administration during the pendency of your review of bioflavonoids?

A. They just sent us bulletins as to what happened with our activities.

Q. But you sent nothing forward to them?

A. No.

Q. Your answer then is that you never did discuss any aspect of the bioflavonoid review with anyone from the FDA?

A. Are you including the sequence of events after you first telephoned me?

Q. No, I am talking about prior to the time your [72] final report was filed.

A. No.

Q. Specifically, did you ever discuss the bioflavenoid matter prior to the filing of your final report with Dr. Ralph Smith of the Food and Drug Administration?

A. No.

Q. As you just mentioned, we have had a couple of conversations by telephone.

Do you remember a telephone conversation we had back—I guess it was—in July, the first time I called you?

A. Yes, I do, vividly.

Q. Why do you remember it so vividly?

A. Because I realized this was going to represent an activity on my part that was going to be of some consequence.

Q. After we spoke did you communicate with any official of the Food and Drug Administration?

A. I did.

Q. Who?

A. I first got in touch with Mr. Drexel, to find out what my next move should be.

Q. He was the Executive Director of the Drug Efficacy Study for the NAS, was he not?

A. Yes.

Q. What did he tell you?

[73] A. He put me in touch with Mr. Goodrich, who subsequently put me in touch with Mrs. Sisk.

Q. Did you discuss with Dr. Drexel or Mr. Drexel what you should do?

Let's back up a moment.

For the record, what did I ask you in our telephone conversation; do you remember?

A. You asked me to make a voluntary deposition on my own.

Q. By that do you mean consent to be interviewed by representatives of USV?

A. I think that is what you intended.

What the legal terminology in this case is, I have no idea.

Q. Did Mr. Drexel give you any advice as to what you should do in response to my request?

A. Mr. Drexel said I would be well-advised to refuse this interview.

Q. Did he give you any reason?

A. Well, he said, first of all, he suspected that I would never be subpoenaed; that by the time this came around that the whole thing would have been dismissed and that I would never be further bothered.

So this was one consideration.

[74] The second consideration is that I felt——

Q. I was asking what Mr. Drexel told you.

A. That is what he told me.

Anyhow, he advised me not to engage in the informal interview you suggested.

Q. What did you then do?

A. I called Mr. Goodrich.

Q. May I ask what he told you?

A. He said the case would probably be dismissed and I would probably not be subpoenaed, but in the event it was, they would give me any advice I required.

Q. Did Mr. Goodrich advise you not to talk to us informally?

A. By the time I got to Mr. Goodrich—I believe, although I am not certain about it—this was already a closed matter.

Q. What was already a closed matter?

A. That I had decided not to talk to you informally.

Q. My question was whether Mr. Goodrich advised you not to talk to us informally?

A. I don't remember.

Q. Why did you decide not to talk to us informally, Dr. Spaet?

A. I felt I should have along with me some legal [75] advice, representing the side of the Food and Drug Administration.

Q. Dr. Spaet, did you do anything prior to this deposition to prepare yourself on the matters you anticipated might be covered?

A. Prior to the deposition?

Q. Yes, prior to our meeting here today?

A. Yes, I did.

Q. May I ask you what that was?

A. Yes, I reviewed the material that I brought with me.

Q. Did you consult with anyone?

A. No. Aside from having telephone conversations with Mrs. Sisk and Mr. Goodrich, no.

Q. May I ask you who initiated those telephone conversations?

A. Well——

Q. How many were there generally, roughly?

A. There was a misunderstanding, I have to tell you.

When I was on vacation, on returning, I had a message that I was called by the Public Health Service.

It turned out that it was you who had called me.

Q. I would like to state that I have never held myself out as a representative of the Public Health Service [76] and I am not now holding myself out in that position.

A. My secretary thought you were Mr. Goodrich.

Q. I am flattered.

A. I promptly called Mr. Goodrich's office, of course, so they knew what was going on, and a conversation ensued relevant to what happened here, and then I also, of course, returned your telephone call.

Q. Prior to coming here today, Dr. Spaet, did you discuss the general nature of your testimony with Mr. Goodrich or Mrs. Sisk or anyone of their colleagues in the Food and Drug Administration?

A. I did.

Mr. HOFFMAN. I have no further questions.

You may cross-examine, Mrs. Sisk.

Mrs. SISK. I wonder if counsel would be agreeable to putting in as an exhibit to this deposition Dr. Spaet's Curriculum Venti Publications which he will supply?

Miss LEVINE. We will be glad to.

#### CROSS-EXAMINATION

By Mrs. SISK:

Q. Dr. Spaet, during the course of the deliberation of the Panel on Hematology and Drug Efficacy Study, was [77] there general discussion or consideration of the use of bioflavonoids in the treatment of bleeding states in man?

A. Yes, there was.

Q. During the course of this consideration, did you find any evidence of efficacy for any bleeding state in man?

A. No.

Q. Did the panel collectively find any evidence of the efficacy of any bioflavonoid for any bleeding state in man?

A. No, they did not. There was no disagreement among the panel.

Q. Dr. Spaet. I have here with me for identification as Defendants' Exhibit A to this deposition Xerox copies of the

relevant pages from the Physician's Desk Reference for 1961, 1962, 1965 and 1966, concerning the product CVP and duo-CVP.

Mrs. SISK. If counsel would like to look at them (handing).

(Xerox copies of relevant pages concerning the products CVP and duo-CVP from Physician's Desk Reference for the years 1961, 1962, 1965 and 1966 marked as Defendants' Exhibits A, B, C and D respectively as of this date.)

[78] By Mrs. SISK:

Q. I want to ask you a few quick questions in your role as an expert in hematology.

Dr. Spaet, do you consider CVP with vitamin K or duo-CVP with vitamin K a safe drug for use in bleeding or hypertension?

A. No, I do not.

Q. Do you consider the product duo-CVP with vitamin K for use as an effective drug in bleeding and hypertension?

A. No, I do not.

Q. Can you tell me, Dr. Spaet, whether or not it is the consensus of expert hematologists that CVP with vitamin K or duo-CVP with vitamin K is generally recognized as safe in the treatment for bleeding or hypertension?

A. They are not.

Q. Can you tell me whether or not, as an expert, you consider CVP with vitamin K or duo-CVP with or without vitamin K to be safe for use in the treatment of diabetes?

A. No, I do not.

Q. Is it your opinion that it is the consensus of opinion between hematologists that this is generally recognized as safe for treatment of diabetes?

A. They are not.

Q. Would your answer be the same for bleeding in [79] retinopathies?

A. Yes.

Q. For bleeding in purpura?

A. Yes.

Miss LEVINE. Would you identify that?

Mrs. SISK. 1961.

By Mrs. SISK:

Q. In threatened and habitual abortion?

A. No.

Q. Bleeding in radiation therapy?

A. Same answer.



Q. Bleeding gums?

A. Same answer.

Q. Bleeding in epistaxis?

A. The same answer.

Q. Bleeding in duodenal ulcer?

A. The same.

Q. And gastrointestinal bleeding?

A. The same.

Q. Will you tell me whether or not this was your opinion in 1961?

A. It was.

Q. Was it the considered opinion of medical men in 1961? [80]

A. It was definitely, among the people working in the field.

Q. How about in 1962?

A. The same.

Q. In 1960?

A. The same.

Q. Let us ask an additional condition, bleeding in menorrhagia?

A. The answer is the same.

Q. And is your testimony the same as to the consensus of opinion among experts?

A. Yes.

Q. Today?

A. Yes.

Q. In 1960?

A. Yes.

Q. 1961?

A. Yes.

Q. 1962?

A. Yes.

Mrs. SISK. I believe that is all the questions that the Government has.

Mr. HOFFMAN. We have a couple on redirect examination.

[81]

#### REDIRECT EXAMINATION

By Miss LEVINE:

Q. Dr. Spaet, you testified a moment ago that the panel generally discussed the efficacy of bioflavonoids in bleeding states in man; is that correct?

A. Yes.

Q. Did the panel specifically discuss the effectiveness of citrus flavonoid compounds in bleeding states in man?

A. It did.



Q. Did the panel specifically discuss the efficacy of citrus flavenoid compound in the reduction of transplacental passage of fetal erythrocytes into the maternal circulation?

A. It did not.

Q. Did it specifically discuss the effect of citrus flavenoids in the reduction of the incidence of intermenstrual bleeding following insertion of intra-uterine contraceptive devices?

A. It did not.

Q. Dr. Spaet, you also testified a few moments ago as to your belief as to what was the consensus of hematology opinions on various matters at various times.

A. Yes.

[82] Q. Where and how did you obtain your knowledge as to what the consensus was?

A. The specific conditions that were noted have been the subject of management publications in large number, using various techniques of management.

Q. You mean patient management?

A. Yes, patient management, and the use of these materials is not a feature of the management. That is, in the authoritative papers on the subject nor in the papers published on the subject in national meetings, nor in the discussions of the subject at seminars and other international conferences in which publication does not emerge.

In other words, being in this field one has the opportunity to have one's ears to the ground as to what people are doing and things with respect to the management of different forms of hemorrhagic states, and if these were considered to be efficacious agents, they would be prominently noted by the major investigators in the field, and they are not.

Q. So it is the absence of reference to citrus flavenoid compound or to bioflavenoid otherwise in these publications, which leads you to the conclusion that the consensus does not recognize the safety and efficacy of these products?

[83] A. In part. Also informally when the bioflavenoids come up and they received a certain amount of publicity in the newspapers, when the FDA first announced the decision with respect to them, I think this must have been a year ago, there was some publicity on it.

Then a good deal of informal discussion on the newspaper reports took place, and one could easily see what the opinion was of people working in the field.

The bioflavonoids were mentioned by people in this field as the drugs in which the FDA was on its firmest ground. This was a direct comment.

Incidentally, one has an opportunity to sample crosses of opinion at national meetings, such as the Federated Society for Experimental Biology, held annually in Atlantic City, and also the meeting designated as the American Society for Clinical Investigation meetings, which brings people from all over the country together in one place. It is around-the-table conversation, which often gives you insight as to where people stand on various subjects.

Since it did receive a certain amount of publicity, this particular group of compounds were specifically discussed.

Q. The discussion you are talking about is discussion within the last year, arising from the FDA's action against [84] the bioflavonoids?

A. That's right.

Q. So it would not have told you anything on the state of consensus in 1962?

A. No. But in 1962 one also had the opportunity to see what was being said and what was new and useful in the management and in the field, in these serious conditions.

Q. The more recent specific statements related to efficacy, however, did they not?

A. Yes.

Q. Not to the safety of the products?

A. They are not unrelated.

Q. Other than the point you made earlier, to the effect that the use of an inefficacious drug you considered it unsafe, other than aspect of safety, these discussions did not relate to safety, did they?

A. Again, I would like to emphasize from a pharmacological viewpoint, I have not heard anybody say this would produce adverse reactions.

I would like to emphasize that the consideration of safety I gave earlier is not a minor one. We consider it a major consequence that a person who has a potentially dangerous situation has his definitive therapy postponed.

[85] Q. This theory would be inapplicable, would it not, in a case where there was no definitive therapy?

A. You never know that unless you investigate the patient.

Q. You mean you don't know whether there is a definitive therapy?

A. You don't know which category into which the patient falls.

Q. In the categories where there is no definitive therapy, however, this consideration is not applicable, is it?

A. There are two forms of therapy that can be efficacious. There is definitive therapy that clears it up finally and also therapy that helps. In other words, a person who has a bleeding disorder can be rendered less severe.

There is a whole spectrum. It is certainly possible that there are patients in the category, who if they got bioflavonoids instead of being properly investigated would not be harmed by it.

In any given patient, you don't know.

Q. If you were to know, however, if you were to determine that there was no definitive therapy or no clearly superior therapy, this consideration of safety would not [86] be applicable, would it?

A. That is true.

Q. Doctor, is it your view that any drug other than the drug of choice is an unsafe drug?

A. Let me rephrase it.

Any treatment other than the treatment of choice is an unsafe treatment, and drug is only a subdivision of this overall category, because therapy would not always be drug.

You people are drug-oriented, of course.

Q. We are not physicians, I regret.

A. If you were in a surgical group and you were to say drug, they would say "what is that?"

Q. Then you would like to broaden the statement to reflect your belief that any treatment which is not the treatment of choice is an unsafe treatment?

A. Yes.

Q. Dr. Spaet, in functional regular menorrhagia, what is the definitive therapy?

A. Well, there is no—let me start all over again. I don't presume. This is a gynecological problem. The situation would be if a gynecologist has a patient who has menorrhagia, he would frequently send such a patient to a hematologist to evaluate whether a hemorrhagic state [87] exists.

If a specific hemorrhagic state can be identified, then the specific therapy for that is undertaken.

On the other hand, if the hematologist can give a clean bill of health for his field, I cannot state how the gynecologist would handle this. It is not in my domain to testify to that.

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

Mr. HOFFMAN. On the record. We have no further questions.

Mrs. SISK. The Government has no further questions.

(Whereupon, at 3:45 p.m. the deposition was concluded.)

Subscribed and sworn to before me this — day of  
\_\_\_\_\_ 1969.

[88]

#### CERTIFICATE

STATE OF NEW YORK,  
County of New York:

I, Charles Richer, a Shorthand Reporter and Commissioner of Deeds of the City of New York, do hereby certify:

That Theodore H. Spaet, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true copy of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage; and that I am in no way interested in the outcome of this matter.

In witness whereof, I have hereunto set my hand this 6th day of October, 1969.

CHARLES RICHER.

[89]

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EXCERPTS FROM TRANSCRIPT OF PROCEEDINGS IN DISTRICT  
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[14] \* \* \*

The COURT. I think you have done a good job so far and I hope you are as cooperative with the rest of it.

Give it to the Clerk, your draft copy. Let the Clerk mark it. Mark it Stipulation as read into the record.

Mr. HOFFMAN. And as modified by the agreements of Counsel.

The COURT. That is right. That is the one that—he will write it all up from there.

Mr. HOFFMAN. Fine.

Mr. EPSTEIN. Thank you, your Honor.

Mr. HOFFMAN. Thank you.

The COURT. I just want it marked Copy for [15] stipulation so that the Reporter will know what it is.

(The stipulation of facts follow:)

Plaintiff and defendants, for the purpose of this action only and without conceding the relevance or admissibility of the following facts, hereby stipulate and agree that:

1. Plaintiff is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business in the State of New York. Plaintiff manufactures and sells drugs in interstate commerce.

2. Plaintiff has manufactured and sold C.V.P. Capsules, C.V.P. Syrup, C.V.P. with Vitamin K Tablets, C.V.P. with Vitamin K Syrup, Duo-C.V.P. Capsules, Duo-C.V.P. with Vitamin K Tablets, Bivam, Prednyl and Prednis-C.V.P., a line of citrus bioflavonoid products, as shown in Exhibit A hereto.

3. The sales figures for C.V.P. products in 1970, based on figures to date and reliable projections to the end of the year are:

Duo-C.V.P. Capsules.....	13,550,000
Duo-C.V.P. with Vitamin K capsules.....	3,565,000
C.V.P. Capsules.....	10,200,000
C.V.P. Syrup.....oz	2,909,396
C.V.P. with Vitamin K Syrup.....oz	119,600
C.V.P. with Vitamin K Tablets.....	5,850,000

4. "Bioflavonoid" is defined in Dorland's illustrated Medical Dictionary, 2nd Edition, as follows: [16] "a generic term for a group of compounds which are widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels."

5. Each C.V.P. Capsule or .5 cc. (Approximately 1 teaspoon)

of C.V.P. Syrup, provides 100 mg. of citrus flavonoid compound of 100 mg. of ascorbic acid (Vitamin C). Each capsule of Duo-C.V.P. provides double these amounts per dose. The dosage recommended in the labeling of C.V.P. capsules is from six to twelve capsules per day. The dosage recommended in the labeling of C.V.P. Syrup and Duo-C.V.P. Capsules provides the same level of bioflavonoids and ascorbic acid as recommended for C.V.P. Capsules. The total daily recommended dose of C.V.P. Capsules, C.V.P. Syrup and Duo C.V.P. provides between 600 and 1,200 mg. of citrus flavonoid compound.

6. Each C.V.P. with Vitamin K Capsule or .5 cc. (approximately 1 teaspoon) dose of C.V.P. with Vitamin K Syrup provides 100 mg. of citrus flavonoid compound, 100 mg. of ascorbic acid and 0.66 mg. menadione (Vitamin K). Each capsule of Duo-C.V.P. with Vitamin K Capsules provides 200 mg. of citrus flavonoid compound, 200 mg. of ascorbic acid and 1 mg. of menadione (Vitamin K). The daily dosage recommended in the labeling of C.V.P. with Vitamin K is from three to fifteen teaspoons or capsules. The daily dosage [17] recommended in the labeling of Duo-C.V.P. with Vitamin K is two to eight capsules. The total daily recommended dose of C.V.P. with Vitamin K capsule, C.V.P. with Vitamin K Syrup, and Duo-C.V.P. with Vitamin K Capsules provides between 300 and 1,600 mg. of citrus flavonoid compound.

7. The daily dose of three tablets recommended in the labeling of Bivam provides:

Citrus Bioflavonoid Compound.....	mg.....	100
Ascorbic Acid (C).....	mg.....	100
Calcium Lactate.....	Gm.....	1
Ferrous Gluconate.....	mg.....	100
Vitamin A.....	U.S.P. Units.....	6000
Vitamin D.....	U.S.P. Units.....	600
Thiamin Mononitrate (B <sub>1</sub> ).....	mg.....	3
Riboflavin (B <sub>2</sub> ).....	mg.....	3
Pyridoxine HCl (B <sub>6</sub> ).....	mg.....	3
Vitamin B <sub>12</sub> (cobalamin conc.).....	mcg.....	3
Niacinamide.....	mg.....	25
d, calcium Pantothenate.....	mg.....	5
Folic Acid.....	mg.....	015
Menadione (K).....	mg.....	1
Vitamin E (dl, Alpha Tocopheryl Acetate).....	Int. Unit.....	1
Magnesium.....	mg.....	3
Manganese.....	mg.....	1
Copper.....	mg.....	1
Zinc.....	mg.....	1
Molybdenum.....	mg.....	0.2
Iodine.....	mg.....	0.1
Cobalt.....	mg.....	0.1

8. Each capsule of Prednis-C.V.P. contains 4 mg. prednisolone (a steroid); 100 mg. citrus flavonoid compound, 100 mg. ascorbic acid; 100 mg. aluminum hydroxide; 100 mg. magnesium oxide. The adult dosage recommended in the labeling of Prednis C.V.P. is two to five capsules daily, providing 200 to 500 mg. of citrus flavonoid compound.

[18] 9. Plaintiff filed new drug applications (NDA's) with the Food and Drug Administration for the foregoing products and they were made effective as follows:

NDA 9065:	Effective date
CVP Capsules.....	Nov. 8, 1955
CVP Syrup.....	Do.
CVP with Vitamin K Syrup.....	Do.
(Supplement):	
CVP with Vitamin K Tablets.....	Jan. 19, 1956
Duo-CVP Capsules.....	
NDA 11474: Prednyl.....	Aug. 26, 1956
NDA 11475: Prednis-CVP.....	Aug. 26, 1956

10. No NDA was ever filed with respect to Duo-C.V.P. with Vitamin K Capsules or Bivam. These two products contain the identical citrus flavonoid compound present in plaintiff's other C.V.P. products.

11. On October 9, 1962, the above products, with the exception of Prednyl which was no longer marketed at that time, were commercially sold and used in the United States.

12. In 1950 in response to a letter inquiry of April 19, 1950, from James B. Redd (copy attached hereto as Exhibit B), FDA by letter of May 31, 1950 (copy attached as Exhibit C) took the position that a product of identical formulation to C.V.P. was not a "new drug" when represented as helpful in increased capillary fragility.

13. By letter of January 3, 1957, the Food and [19] Drug Administration communicated to plaintiff its opinion that Bivam was not a new drug when distributed under labeling recommending its use as a dietary supplement. A copy of this letter is attached hereto as Exhibit D.

15. By letter of April 19, 1961, the Food and Drug Administration communicated to plaintiff its opinion that Prednyl and Prednis-C.V.P. (combinations of CVP and a steroid) were not new drugs when distributed under the labeling provided for in NDA 11474 and NDA 11475, respectively, in the dosages set forth above, which recommended their use in the treatment



of capillary fragility and permeability. The citrus flavonoid compound in Prednyl and Prednis-C.V.P. is identical to the citrus flavonoid compound in plaintiff's other C.V.P. products. A copy of this letter is attached hereto as Exhibit E.

[25] \* \* \* \*

Mr. HOFFMAN. We would like him to admit that in December, 1957, FDA was not concerned about the safety, per se, of the C.V.P. products.

The COURT. He could not—I will tell him not to admit that because I do not know that it is relevant, whether they were or were not. How can he speak for FDA?

Next question.

I mean clearly that is a conclusion. He could not speak for them if he wanted to and bind the Government.

Mr. HOFFMAN. Your Honor, he was their counsel speaking for the Commissioner for FDA.

The COURT. That does not make any difference. I understand. But a lot of counsel do not know what their clients have in mind sometimes.

Mr. HOFFMAN. Your Honor, we respectfully except to that ruling.

The COURT. You may except to it, and I do not know—what relevance does it have on you whether they were interested in it in 1896 or 1957? What difference does it make?

Mr. HOFFMAN. Your Honor, it is our position that it was the business of the Food and Drug Administration in 1957 and has been since to determine among other things [26] whether there is substantial evidence or, for example, of safety of products.

The COURT. Wait a minute. You are arguing the case.

Mr. HOFFMAN. And that is expert opinion.

The COURT. Mr. Hoffman, you are arguing. I am sure he will stipulate if you want him to do that in 1957 the FDA had not in fact taken any affirmative action. Now, it does not make any difference why they had not done it.

They had not done it. Isn't that correct, Mr. Epstein?

Mr. EPSTEIN. That is correct, your Honor.

The COURT. All right. It is stipulated they did not do it. It does not make any difference why they did not do it. They took no action in 1957.

Mr. HOFFMAN. Your Honor, the other fact that we believe they have already stipulated to—



The COURT. Now you may argue what that means later.  
All right.

Mr. HOFFMAN. Your Honor, the other fact that we think they have already agreed to and would like them to agree to now is that as stated in their previously filed documents on or before October 9, 1962, and at all times since it was and is generally recognized by experts qualified by [27] scientific training and experience to evaluate the safety of drugs that citrus flavonoid compounds, that is bioflavonoid, when used in the dosage recommended for Plaintiff's products are not pharmacologically toxic in that a normal individual given these agents would not develop adverse reactions.

The COURT. All right.

Are you willing to stipulate that in your opinion, whatever that means, that experts would so testify if they were called?

Mr. HOFFMAN. Are you addressing that to Mr. Epstein?

The COURT. Yes, I am addressing it to him.

Mr. HOFFMAN. Your Honor, the——

The COURT. Wait a minute. That is all that says.

Are you willing to admit that experts, if they were called, would so testify——

Mr. HOFFMAN. Your Honor, I am reading——

The COURT (continuing). They are non-toxic.

Mr. HOFFMAN. I am reading from their statement.

The COURT. It does not make any difference. I now want to know it.

Mr. EPSTEIN. Your Honor, may I have just a moment to confer with the Doctor?

[28] The COURT. Yes. If not, you may put a doctor on and let him testify and we will get to that real quick.

What you are stipulating is that experts would say that these citrus or bio——what do you call them?

Mr. HOFFMAN. Bioflavonoids, your Honor.

The COURT (continuing). Bioflavonoids are not toxic when used in accordance with your prescription or your labeling, whatever you call it.

Mr. HOFFMAN. That is what they said before.

The COURT. That does not make it a fact. It is just an expert opinion that would say that.

Mr. HOFFMAN. That is exactly right, your Honor, and it is the statement——

The COURT. Expert opinions unfortunately are not always correct.

Mr. HOFFMAN. It is the state of the expert opinion, not the underlying fact that is the issue in this case, your Honor.

Mr. EPSTEIN. Your Honor, my difficulty—

The COURT. Just tell me yes or no. I do not want any difficulty. I mean really I am going to get to this.

Mr. EPSTEIN. All right.

The COURT. Are you satisfied that if experts were called they would testify to that statement?

Mr. EPSTEIN. Yes, they would, your Honor.

[29] The COURT. All right.

Mr. EPSTEIN. We will so stipulate.

[76] \* \* \*

Mr. EPSTEIN. The government calls as its first witness, your Honor, Dr. Theodore H. Spaet.

The COURT. Step forward, Doctor.

Whereupon,

Theodore H. Spaet was called as a witness, and having been first duly sworn, was examined and testified as follows:

[85] \* \* \*

By Mr. EPSTEIN:

Q. What are bioflavonoids, Dr. Spaet?

A. Bioflavonoids are materials extracted, basically extracted from various vegetable material but mostly fruit skins.

The COURT. Mostly fruit skins?

The WITNESS. Citrus fruit skins, that is right. [86] There are special chemicals that emerge in the extraction procedure.

[89] \* \* \* The COURT. First do you have the committee opinion?

Mr. EPSTEIN. Your Honor, I do not have the committee's written opinion.

The COURT. Then you can't offer it.

Mr. EPSTEIN. That is why I am asking him specifically of his own opinion.

The COURT. All right. If you have it I will let you offer it.

But he doesn't have it, he says.

Mr. HOFFMAN. Objection, your Honor.

Mr. EPSTEIN. Well, may I say——

Mr. HOFFMAN. His opinion is not relevant, the opinion of any particular expert is not relevant. The only issue would be the state of the expert consensus, not Dr. Spaet's or any other particular individual.

The COURT. Objection is overruled. It again goes to the weight of it. He can give his own opinion.

By Mr. EPSTEIN:

Q. What is your opinion on the plaintiff's bioflavonoid drugs, your Honor,—a—Dr. Spaet?

A. In my opinion the bioflavonoids as produced by the plaintiff have no demonstrated value in the treatment of bleeding disorders.

[90] Q. Doctor, is that opinion concurred in by your colleagues who are also experts in the field of hematology?

A. To the best of my knowledge this is virtually a universal rule among the people who are generally classified as my colleagues in this area.

Q. Has that view been communicated to you in the forms of discussions with your—

The COURT. Let's get to the meat of it.

Mr. EPSTEIN. All right.

The COURT. How many other doctors roughly in your field have you discussed the plaintiff's drug in question with, roughly?

The WITNESS. Well, I couldn't name the number with whom I have discussed it. But——

The COURT. Say approximately,——

The WITNESS (continuing). Possibly——

The COURT (continuing). One, ten, twenty——

The WITNESS (continuing). Possibly ten.

The COURT. All right. And of those ten that you discussed it with them, did any of them, either disagree or expressly agree with the opinions that you said that it had no effect?

The WITNESS. No, your Honor.

The COURT. What did they do?

The WITNESS. Well, we generally laughed about it.

[91] The COURT. You just laughed?

The WITNESS. Yes.

The COURT. So they expressed no opinion?

The WITNESS. No, no. They agreed with me, sir.

The COURT. How did they agree with you? Did they say you are correct, or just laugh?

The WITNESS. No. They say that—they conveyed to me that I am correct. I don't remember their exact words, your Honor.

The COURT. You got the impression from them that they didn't disagree with your opinion?

The WITNESS. That they agreed with it most heartily, your Honor.

The COURT. All right. That is about 10.

Let's take it from there.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration of the plaintiff's bioflavonoid products to a patient who may be evidencing the symptoms of habitual and threatened abortion is a safe modality for the treatment of that condition?

A. I do not.

Mr. HOFFMAN. Your Honor, I object to that question on the grounds that there has been no showing that any of plaintiff's products are recommended for the treatment of threatened abortion rather than for the treatment of [92] capillary fragility when it occurs.

The COURT. I will allow you to cross-examine him. He is an expert. You can show that he is talking about something that does not effect you. That is the purpose of cross-examination.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration of plaintiffs' products to a patient who is suffering from post-partum bleeding is a safe modality for the treatment of that condition?

Mr. HOFFMAN. Same objection, your Honor.

The COURT. Objection is overruled.

The WITNESS. May I give my answer?

The COURT. Sure.

The WITNESS. I think it is not safe, your Honor.

By Mr. EPSTEIN:

Q. Would you tell us why it is not safe, Dr. Spaet?

A. Yes, because it precludes the use of the appropriate treatment in the patient who has a major problem. If a drug is inefficacious and it is being used instead of an efficacious agent then it is not safe.

The COURT. If it is harmless what difference is there to keep you from using both of them?

The WITNESS. But the point is if the agent——

The COURT. Oh, no. I just want you to explain [93] to me.

The WITNESS. Yes, sir.

The COURT. You said it has no affect period, it was useless; that is like a placebo—and you know what a placebo is I am sure.

The WITNESS. Yes, sir.

The COURT. Because you give me a placebo, which is nothing but sugar water, or whatever you want to call it, just to satisfy my vanity, that wouldn't interfere with giving me a pill that would do me some good, would it?

The WITNESS. May I illustrate, your Honor?

The COURT. Well, answer it, first.

The WITNESS. My answer is that it is like putting tap water in your radiator, car radiator in the middle of winter. Now, this doesn't hurt the radiator as such, but it is not safe to do it.

The COURT. If I put tap water in a radiator and I also put Zerex, I would have a pretty good radiator, wouldn't I?

The WITNESS. If you filled your radiator with tap water there would be no room for the Zerex.

The COURT. Now, that is—now you are getting at it. The question is: is this harmful, not that—and I understood you to say that it interfered with putting in, putting tap water, as you call it, in a radiator, wouldn't [94] interfere with putting Zerex unless I filled it up, would it?

The WITNESS. If tap water is offered as the efficacious way of preventing your radiator from freezing over, then an individual convinced of this would not put in the Zerex.

The COURT. Well, that is debatable.

The WITNESS. I think that——

The COURT. I understand what you are saying.

The WITNESS (continuing). There are some who wouldn't.

The COURT. You are just saying that if I took so many placebos that I couldn't hold any other pills then I wouldn't get the benefit of the other pill; isn't that what you are saying?

The WITNESS. No, your Honor, that is not quite what I am saying.

The COURT. What are you saying?

The WITNESS. What I am saying is that if a physician feels that he has an efficacious agent and gives it to a patient to stop bleeding he may use this instead of the efficacious agent.

The COURT. He may, and he would not get the bleeding stopped.

The WITNESS. He would not get the bleeding stopped and a very dangerous consequence.

The COURT. And it wouldn't be the proper [95] treatment.

The WITNESS. That is right.

The COURT. But it wouldn't show that this was a—it might show false labeling or false advertising, but it wouldn't show that this was a harmful drug, that it would cause harm.

The WITNESS. Well, can I tell you about my own experience in this respect?

The COURT. Sure.

Mr. HOFFMAN. We object, your Honor, on the ground that his experience is not relevant. It is general recognition.

The COURT. If his experience isn't relevant to forming an opinion, I don't know what is.

Mr. HOFFMAN. Your Honor, what would be would be his testimony such as he gave before on what the expert consensus is as to the safety of the product, not—

The COURT. Objection is overruled. I do not know of any better experience that a doctor or a lawyer gets than 40 years of his own practice. It is far more important to him than it is all the journals he can read.

Now, let's get on with it.

You practice law and the more you practice the more experienced you get, and you base your future on the mistakes you made in the past and hope you don't make them [96] again.

Next question.

Mr. HOFFMAN. Your Honor, could we direct the Court's attention to certain judicial decisions dealing with precisely this issue of the difference between general recognition, on the one hand, and the witness' own experience?

The COURT. We are not talking about general recognition. We are talking about this man's expertise.

Mr. HOFFMAN. These are the cases that say that is irrelevant, your Honor.

The COURT. Well, I don't think it is.

By Mr. EPSTEIN:

Q. Go ahead, Dr. Spaet.

A. Your Honor, I had a patient not too long ago who had a tonsillectomy. He had hemophilia. The tonsillectomy should not have been done. The doctor who did it gave this boy, who was bleeding for days, inefficacious agents, and when he came to me he was almost dead because the proper treatment had not been given. The reason is that this physician had been told by various sources, not appropriate ones, but by various sources that if you give A and you give B and you give C everything will be all right. Now, I think it is dangerous to tell physicians this. I think a drug that is offered as an efficacious agent in serious conditions and that does not have this effect is not a safe drug.

[97] Mr. HOFFMAN. Your Honor, we move that that testimony be stricken on the ground that there is no showing that the product that the young person in question was being given was one of the products involved in this case. We think that it is prejudicial.

The COURT. He has just said that if it wasn't properly labeled—you see you are getting excited too easy. He didn't say that your drug was improperly labeled. If you don't ask him I am—I mean about your drug—that is all I want to know.

By Mr. EPSTEIN:

Q. Dr. Spaet, is the opinion that you have just given the opinion that is shared in by your colleagues in the specialty of hematology and internal medicine?

A. I think it is.

The COURT. I want to know about this person's drug. I am still not talking about A, B, C and D. We are not trying A, B, C and D. We are determining the efficacy of this drug.

Do you understand, Doctor?

The WITNESS. I do.

The COURT. Not anybody else's. Now, let's get—

The WITNESS. I was just trying to illustrate, your Honor.

The COURT. But it has really no weight. Because [98] B and C is no good doesn't make A bad, does it? Obviously not.

The WITNESS. No. I was trying to illustrate why lack of efficacy could also mean lack of safety.

The COURT. I understand.

Mr. EPSTEIN. And my question, your Honor, was when I asked him the first question was: was it the use of plaintiff's drugs, was it the administration of the plaintiff's drugs?

The COURT. He hasn't talked about plaintiff's drugs. He is talking about A, B and C. Get him to plaintiff's drugs. Get him on plaintiff's drugs if you want to do that.

By Mr. EPSTEIN:

Q. Dr. Spaet, is it your opinion that the administration of the plaintiff's products to a patient who has just had a tonsillectomy would be a safe modality for the treatment of the bleeding condition that results from a tonsillectomy?

A. I do not believe it would.

Q. Would you tell us why not, Dr. Spaet?

A. Because if a patient is bleeding following a tonsillectomy he requires whatever the treatment is appropriate for his underlying reason for bleeding, not bioflavonoids.

Q. Is this opinion shared in by your colleagues, Dr. Spaet?

[99] A. I believe it is.

Q. Is it your opinion that the administration of the plaintiff's products to a patient who is suffering from hypertension is a safe modality for the treatment of that condition with plaintiff's products?

A. The same answer applies.

Q. Is that opinion also shared in by your colleagues, Dr. Spaet?

A. The same answer applies.

Q. Is it your opinion—well, without going through the whole length of the question, let me just say I am asking him the same question again, your Honor, and I am applying the plaintiff's products in use in a situation where there are "little strokes" as defined in the plaintiff's labeling. Would you use the plaintiff's products in that kind of a patient, your Honor,—Doctor?

A. I would not and I do not think it is a safe modality for use in it.

Q. And is this opinion shared in by your colleagues, Dr. Spaet?

A. I believe it is.

Q. Now, Dr. Spaet, how about using the plaintiff's products in connection with a diabetic retinitis?

Mr. HOFFMAN. Objection, your Honor. He is not specifying which of the products involved in this case he is [99-A] talking about. There are six, or seven or eight products, and the questions are being framed universally; the doctor is responding universally.



The COURT. I am not going to exercise any tighter control on this case than I have. If the government puts on weak evidence you take the advantage of it; if they put on strong evidence you rebut it. Now, if you—I will agree with you: his testimony is a little vague and indefinite, and I have suggested a dozen times—I mean to counsel, not the doctor, that it will have more weight with me if he talks about A, B and C instead of talking about generalities. That is up to counsel. And I agree that you have more than one drug involved here.

Mr. EPSTEIN. The problem is, your Honor—

The COURT. If his testimony is generally they are not good for any of the purposes for which the label says they are let him say so, and then he can bring out they are good—if he says that they are harmful for everything set forth on the label, you want to generalize it, let him do it.

Mr. EPSTEIN. But the generality only went because they are all bioflavonoid products that we are dealing with, and I thought that the doctor had already told us that he was using—his answer applied to the use of bioflavonoids, but I will specify with each of the products, then, your Honor, so we will have that clear.

[99-B] The COURT. I mean if there is any dispute, and again let's get this—

Mr. EPSTEIN. Yes.

The COURT (continuing). If the doctor is familiar with the labels in question here on the drugs here involved, all he's got to do is to say, "I have read that label, I am familiar with it, and in my opinion this drug will not accomplish any of those purposes," if that is his answer. I don't know what his answer is.

By Mr. EPSTEIN:

Q. Dr. Spaet, are you familiar with the labeling and the representations that are made for the plaintiff's C.V.P. capsules?

A. I am.

Q. Are you familiar with the labeling—

The COURT. Let's take those capsules and let him say what—he says he is familiar with them. Now ask him a question about them.

Mr. EPSTEIN. All right.

By Mr. EPSTEIN:

Q. Doctor, would you use——

The COURT. Not would he use.

Mr. EPSTEIN. Excuse me.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration [99-C] of the plaintiff's C.V.P. capsules to a patient who is suffering or who has a condition of habitual and threatened abortion would be a safe modality for the treatment of that condition?

A. I believe it would not.

The COURT. Does the label say it would, in your opinion?

The WITNESS. The label in my opinion says that it is offered for the treatment of it.

The COURT. All right.

Mr. HOFFMAN. Objection, your Honor. He is not qualified as an expert in the meaning of the labeling. But in any event we think the court should determine that.

The COURT. I will say this much, if he is not labels are not worth the paper they are written on.

Mr. HOFFMAN. Your Honor, we think the court can determine what the labeling means, not this witness.

The COURT. I am not as expert as he is. If you use big language I don't know how I am going to know whether this pill is good for bleeding from abortions or whether it isn't if an expert doesn't tell me.

Mr. HOFFMAN. Your Honor, the question was not whether the product would be good for that condition. The question was whether that is what the labeling recommended it for.

[99-D] The COURT. Well, he says it does.

Mr. HOFFMAN. That is the determinative piece of paper.

The COURT. He says it does. Now, you point out—let him show you as an expert where it doesn't say that.

All right. Go ahead.

By Mr. EPSTEIN:

Q. Doctor, why would you not use the plaintiff's products C.V.P. capsules for a patient who is suffering from the problem of habitual and threatened abortion?

A. Because the efficacious therapy for that is other and again by using this you are relying on something——

The COURT. Doctor, so we get this, there may be better, that is not the question in this case——

The WITNESS. No, your Honor; other.

The COURT. I say there may be other methods of treating it. The question is whether or not basically this is false labeling, whether or not the drug, it will not do what it says; the mere fact that another drug—in other words, doctors might agree that aspirin and Bufferin, which are technically two different labeled products, both might be proper for a simple headache—do you follow what I mean?

The WITNESS. I do, sir.

The COURT. That is what I am referring to here, so let's confine it to this drug, tell him why it is either no [99-E] good or harmful, whichever it might be, in the treatment for bleeding following abortion.

The WITNESS. On the basis of the available literature, sir—

The COURT. All right.

The WITNESS (continuing). The evidence that it is of benefit is far from adequate; it is inadequate in my opinion.

The COURT. All right.

The WITNESS. Now, the same principles that I have been applying in other conditions, I believe, sir, apply here as well, that if you have an inefficacious product in an attempt to treat a major illness and use that instead of an available method that is efficacious, then the use of this product, the offering of it is a danger insofar as the efficacious therapy is being forestalled.

The COURT. You leave that argument to your counsel.

The WITNESS. Okay.

The COURT. I mean now we just want to get the facts. You may be on sound ground, see, but your factual evidence is that in your opinion, based on experience and based on medical literature, that this capsule just mentioned would have no therapeutic or curative effect on the ailment referred to.

The WITNESS. Yes, sir.

[99-F] The COURT. That is a fact, in your opinion, so let's limit your testimony to facts.

By Mr. EPSTEIN:

Q. Doctor, is the opinion that you have just described to us the opinion shared by your colleagues?

The COURT. He said it was.

Mr. EPSTEIN. All right.

By Mr. EPSTEIN:

Q. Now, Doctor, as to the plaintiff's C.V.P. capsules, is it your opinion that the administration of the plaintiff's C.V.P.

capsules to a patient who is suffering from postpartum bleeding would be a safe modality for the treatment of that condition in that patient?

A. The same answer applies.

Q. Would you tell us why, Dr. Spaet?

A. Well, again, the studies that are available——

The COURT. If your answer, Doctor, and I don't want to cut you off, if your answer is although it is harmless it doesn't accomplish the purpose the label says it does, just say that.

The WITNESS. The same answer applies as before, basically.

The COURT. He just says it is like tap water, it is harmless, but it won't grant any relief.

Is that correct?

[99-G] The WITNESS. Yes, sir.

The COURT. All right. We will take it from there.

By Mr. EPSTEIN:

Q. Doctor, referring to the plaintiff's C.V.P. Capsules, is it your opinion that the administration of the plaintiff's C.V.P. Capsules to a patient who may be suffering from epistaxis is a safe modality for the treatment of that condition?

A. I do not.

Q. Would you tell us why not, Dr. Spaet?

A. The same answer applies as before.

Q. Is that opinion also shared by your colleagues?

A. To the best of my knowledge.

Q. As to the C.V.P. Capsules, is it your opinion that the administration of plaintiff's C.V.P. Capsules to a patient who is suffering from diabetic retinitis would be a safe modality for the treatment of that condition?

A. I do not.

Q. Would you tell us why not, Doctor?

A. The same answer applies.

Q. What is diabetic retinitis, sir?

A. These are changes in the retina of the eye that are a consequence of the underlying diabetic condition.

Q. What kind of treatment do you administer to [99-H] a diabetic, Doctor?

The COURT. No. I do not want him to go into that.

Mr. EPSTEIN. All right.

The COURT. It isn't necessary.

Mr. EPSTEIN. Your Honor, then I will just go to each of the specific questions.

**By Mr. EPSTEIN:**

Q. Dr. Spaet, is this opinion that you just stated the opinion that is shared by your colleagues?

A. To the best of my knowledge.

Q. Is it your opinion that the administration of plaintiff's C.V.P. Capsules to a patient who is suffering from an ocular disorder is the safe modality for the treatment of that condition?

A. I do not.

Q. Would you tell us why not, Doctor?

A. Because the same answer applies as before. Your Honor, should I go through it separately each time?

The COURT. Not if it is the same answer.

The WITNESS. It is basically the same answer.

The COURT. And I understand your answer to be, Doctor, on each of these, and I follow your reasoning, that the label that the company puts out for this capsule would indicate to the average doctor that it was effective [99-I] in the curative of that particular ailment?

The WITNESS. Yes, sir.

The COURT. All right. Now if that applies to each one of them you can say it as to all of them to save time. But I just want to make sure that the label says to this doctor it will do that and in his opinion and in the opinion of his colleagues it is not only won't do it, it is unsafe because it keeps a doctor by this false advertising from using what otherwise he would have used.

Is that what you are saying?

The WITNESS. All right. Now, that applies to all of them; then he can find out why, what is wrong with this.

**By Mr. EPSTEIN:**

Q. I will ask you, then, the same question, Dr. Spaet, as it applies to a patient who has menorrhagia?

A. Yes, sir, it is the same answer.

Q. How about Rh incompatibility?

A. Same answer.

Q. And rheumatoid arthritis?

A. Same answer.

Q. And hemorrhagic duodenal ulcer?

A. Same answer.

Q. And ulcerative colitis?

A. Same answer.

Q. And hemorrhagic cystitis?

[99-J] A. Same answer.

Q. Postoperative bleeding?

A. Same answer.

Q. Radiation therapy?

A. Same answer.

Q. Now, I will ask you the same list of questions, Dr. Spaet, for the same conditions, and I will ask you is it safe to use plaintiff's product Duo-C.V.P. for the same disorders and the same line of questioning?

A. Same answer.

Q. And is this opinion also shared in by your colleagues?

A. To the best of my knowledge.

Q. I will ask you if the same is true for plaintiff's product C.V.P. with K?

A. Same answer.

Q. And you would give the same answer for each of the disorders or physical illnesses which we have gone through in this specific list on the use of their products?

A. I would.

Q. As to for the use of plaintiff's product Duo-C.V.P. with K?

A. Same answer.

Q. And to the same list of conditions which I have described from the previous line of questioning?

[99-K] A. Yes.

Q. And would those opinions be shared in by your colleagues?

A. I believe so.

Q. And as to Duo-C.V.P. or——

(Mr. Epstein conferred with his co-counsel.)

Mr. EPSTEIN. All right. Excuse me a minute. Did I understand your Honor to say that you did not want to go into what would be the therapy of choice in various of these disorders, you were not going into.

The COURT. I don't think we need that evidence.

Mr. EPSTEIN. Yes.

The COURT. If you have three choices of a remedy one doctor might use one and one might use the other. I mean that is common practice.

Mr. EPSTEIN. Yes.

The COURT. I understand his theory is that by using this method—

Mr. EPSTEIN. That is right.

The COURT—It precludes the doctor from using a proper method.

Mr. EPSTEIN. Right.

The COURT. And, therefore, it is harmful. That is what he is saying.

Mr. EPSTEIN. Right.

[99-L] The COURT. Aren't you, Doctor?

The WITNESS. Yes, sir.

By Mr. EPSTEIN:

Q. Dr. Spaet, what is capillary permeability?

A. That is the ability of the capillary to allow normal constituents of the blood to pass through it, to nourish the tissues.

Q. In your opinion is it sound medical judgment to eliminate or remove capillary permeability or decreased capillary permeability?

A. No.

Q. Would you tell us why?

A. Capillary permeability is the means whereby things are transported from the blood to the tissue and if you remove this, of course, then everything we go by is eliminated, all the traffic stops.

Q. What is capillary fragility?

A. Yes. This is the liability that the capillaries have to rupture; in other words, how easily you can rupture capillaries is a measure of their fragility.

Q. Let me ask this, then: If an individual were brought to you and you were told that he had abnormal capillary fragility, what is the medical significance of his state?

A. This means that he has a likelihood of being more susceptible to bleeding.

[99-M] Q. If he is more susceptible to bleeding, do you treat the capillaries or give a treatment for the capillaries in this individual who would be susceptible to bleeding?

A. Not as such. You treat the underlying condition that is causing it.

Q. How do you establish this underlying condition?

A. By a series of diagnostic tests that we have available to us.

Q. What are the causes of capillary fragility and capillary permeability?

A. It can be caused by scurvy. It can be caused by diabetes. It can be caused by allergies. It can be caused by a whole host of things.

The COURT. Excuse me. This is most interesting and I love a medical education. Sometimes it saves me going to a doctor and when it does I get in trouble, because I don't remember it just right. But seriously, what has this got to do with this case? And you say his label says that use my drug, my capsule and you will be cured of capillary fragility? Do you say that is what his label says?

Mr. EPSTEIN. Yes.

The COURT. Ask him if his label includes that and is it curative or harmful for it.

Mr. EPSTEIN. Well, I completely——

The COURT. That is the question.

[99-N] Mr. EPSTEIN. Yes. The labeling is already in evidence, your Honor. It has been agreed to.

The COURT. I know, but I may not be able to read it. I want an expert to tell me what it says.

Does the label on his drugs—I will ask you. He doesn't want to find out. Do these labels to a doctor——

The WITNESS. Yes.

The COURT (continuing). Clearly indicate that the use of these drugs will cure or have a curative effect on this capillary fragility that he has been describing?

The WITNESS. Irrespective of cause almost.

The COURT. What?

The WITNESS. Almost irrespective of cause.

The COURT. And the label says that?

The WITNESS. Yes.

The COURT. And you disagree with that?

Mr. HOFFMAN. Your Honor, we think the document speaks for itself.

The COURT. I will let you examine him what the label says. What?

Mr. HOFFMAN. We think the document speaks for itself.

The COURT. You can ask him to point out if you don't think it says that.

Mr. HOFFMAN. We will, your Honor.



[99-O] The COURT. All right. You can ask him what language is in the label. Get it out and show it to him, and I will look at it at the same time.

He says that, and he says it has the same effect as these other drugs, none—it is harmful.

Next question.

By Mr. EPSTEIN:

Q. Doctor, in summary to all of these specific questions that we have asked, do you—is it your opinion that it is medically safe to use the plaintiff's bioflavonoid products for altering capillary permeability and/or capillary fragility or in the treatment of any of the diseases and conditions that are prescribed, recommended or suggested in the various items of written matter, printed or graphic descriptions of the plaintiff's products?

A. It is my opinion that across the board these are neither efficacious nor safe.

Q. Was this your opinion, did you hold this opinion also, Dr. Spaet, on October 9, 1962?

A. I did.

Q. And do you hold that opinion today?

A. I do.

Q. Is that opinion concurred in by your colleagues also?

A. As far as I know.

[99-P] Q. And can you tell us whether your colleagues also concurred in that opinion on October 9, 1962?

A. To the best of my knowledge.

Mr. EPSTEIN. I have no further questions on direct, your Honor.

The COURT. All right. You may cross-examine him, and he is an expert, so I will allow you to bring out anything that you disagree with, but I will ask him one question first.

Doctor, from some of the exhibits, and I don't remember the figures, but speaking in quantities apparently they are distributed and sold quite a bit, a large quantities of this medication.

The WITNESS. Yes, sir, your Honor.

The COURT. Are you familiar with the relative amounts that they have alleged to have sold?

The WITNESS. I understand that the sales are something like \$5 million a year, or something like that.

The COURT. My question is what explanation, if any, do you have to offer why practicing doctors throughout the country

would continue to use these drugs for these purposes if the results therefrom turned out to be in their patients what you have just indicated is the result? Why do doctors keep on using pills for eight years when experience should teach them if that is the result that it has absolutely [99-Q] no effect on the patient?

The WITNESS. Your Honor, would you like me to speculate?

The COURT. No. I want you to speak as a doctor if you can answer the question. I don't want any speculation. If you know.

The WITNESS. I don't know the answer to it, but I know that it is a wide-spread phenomenon that is well known throughout history.

Mr. HOFFMAN. I object to this line, your Honor. It is speculation.

The COURT. You may object. I want to get information.

Elaborate a little.

The WITNESS. Well, we know that inefficacious views as to explanations for things or how to achieve things have been held as long as man has records. The efficacy of magic, for example, was held by societies from time immemorial—why they were convinced that it worked.

The COURT. But it ceases to exist after a time, doesn't it?

The WITNESS. Well, eons.

The COURT. We have—most of us have quit witchcraft.

The WITNESS. But look how long it took us, your [99-R] Honor.

The COURT. I mean—well, no—I just asked you. Give the answer eight years isn't long enough to satisfy the average doctor. Is that what you mean?

The WITNESS. What I mean is that I can give what I consider—

The COURT. No. I mean I want to get your reasoning. As to witchcraft, it is time you are saying; magic is time.

The WITNESS. Yes.

The COURT. Of course a lot of things doctors do today they didn't do 10 years ago.

The WITNESS. That is right, sir.

The COURT. It is continually changing in the practice.

The WITNESS. I will tell you—

The COURT. How long does it take a doctor, the average good doctor, to find out, based on his own experience, that a pill advertised to stop bleeding, and that is what this is reduced to simplicity, or curtail bleeding, isn't that right?

The WITNESS. That is right, sir.

The COURT. How long does it take a doctor with bleeding patients to find out the pill doesn't produce the desired result—eight years, two years, five years, thirty years?

[99-S] The WITNESS. I think that with some doctors it takes replacement of that doctor.

The COURT. In other words, you say that the doctor then is in your opinion gullible from the pharmaceutical house and will accept anything they say?

The WITNESS. Also I think that that doctor may have had a good experience in which he gave such a medication to a patient early in the game, the patient stopped bleeding perhaps for reasons that had completely nothing to do with the agent, and he said, "Ah," and then everytime something like this comes along he tries it again.

The COURT. That would not be the situation in \$5 million worth, would it?

Mr. HOFFMAN. Your Honor, I object to this as speculation and not tied to the—

The COURT. I understand, but I want to do a little speculation.

The WITNESS. It is admittedly so.

Mr. HOFFMAN. Note a continuing objection.

The COURT. I mean I—seriously I want to find out. This is favorable to you and you want to cut it off. I really want to know why doctors do this because the evidence shows they do it, and then I want to know why the Government doesn't send out labels "Don't use these pills," or why they don't take them off and why it takes the government eight years. [99-T] There are a lot of things I want to know.

The WITNESS. Your Honor—

The COURT. Why it takes them eight years to stop something that you knew in 1962, when you served with the committee in '68, and they haven't issued any orders to cease and desist, as far as I know. These are questions they are getting to get answer for me.

All right.

The WITNESS. Your Honor, I have been involved in the whole process of how to get up-to-date medicine in the hands of people who are not associated with a teaching institution. At the New York Academy of Medicine this was one of our major problems.

We found that no matter what you do there is a group of physicians whom you cannot reach. You cannot reach them by television, you cannot reach them by any of the means that we normally—

The COURT. Do I understand that these pills are only being used by that class of doctor?

The WITNESS. I think so, sir.

The COURT. They are not being used generally by doctors in the field according to your experience?

The WITNESS. I do not know—

The COURT. They are not being used generally by reputable doctors?

The WITNESS. I do not know that they are on [99-U] the pharmacy list.

The COURT. Do you know anybody who uses them?

The WITNESS. No, sir.

The COURT. Do you know anybody that has ever used them?

The WITNESS. No, sir.

The COURT. Have you ever talked to a doctor, you or the committee, that has ever used them to determine what the results were?

The WITNESS. To the individual physicians, no, sir.

The COURT. Did you ever send a questionnaire out as a committee or anything to the doctors that were known to be using these pills for the purpose of getting their experiences?

\* \* \* \*

[100] (AFTER RECESS)

[Whereupon, Theodore Spaet, the witness on the stand at the time of recess, resumed the stand, was examined and testified further as follows:]

The COURT. So that I will be fully informed, and maybe the counsel can stipulate this, are these drugs—I am talking about the ones in issue here—are they dispensed, in the main, through doctors, or are they dispensed, in the main, to the public absent doctors, which are they, or both?

Mr. HOFFMAN. Your Honor, the products are available, with labeling that simply says it is a dietary supplement, and it says nothing more than that, over the counter. The only information suggesting that the products are useable in abnormal capillary fragility and permeability, specifically, the only label-

ing involved in this case is labeling that is available to physicians. As to that use, it is a prescription product and we are not concerned with any use of the product that is in this case that is not a prescription product. I believe the government will stipulate that.

The COURT. That is what I was getting at. These are prescription; in other words, they are dispensed through doctors?

Mr. EPSTEIN. Yes, sir.

[101] The COURT. All right. I just wanted to make sure.

Mr. EPSTEIN. We will stipulate they are dispensed through physician prescriptions, Your Honor.

The COURT. That is right. All right. And it is an alleged mislabeling, as far as the doctor is concerned, and not a new drug, as far as they are concerned. I understand.

All right.

#### CROSS EXAMINATION

By Mr. HOFFMAN:

Q. Good afternoon, Dr. Spaet. Dr. Spaet, I believe you testified on direct examination that you had not heard of the C.V.P. products, that is, the products involved in this case, until about 1966; is that correct?

A. Yes, sir.

Q. I believe you also testified—

The COURT. Wait a minute. I did not understand that. He said he knew of this situation in 1962.

Mr. HOFFMAN. Your Honor, I was just getting to that.

The COURT. That is what he said.

Now, you gave your opinion that these had that effect in 1962; is that correct?

The WITNESS. I was not made familiar, Your Honor, [102] the bioflavonoids of this company until 1966, when I sat on the Drug Efficacy Committee.

The COURT. All right. Then his knowledge of it will be limited to 1966. He said he was not familiar with it.

Mr. EPSTEIN. Your Honor, let me just try and straighten one important issue out on that subject. The thing that the doctor testified was as to what bioflavonoids are. The government and counsel for the plaintiffs have already stipulated what these products contain. That is already in evidence.

The COURT. We understand that.

Mr. EPSTEIN. Because my important consideration here is that Dr. Spaet, as an expert in this area, did know about bioflavonoids, and bioflavonoids fall in the same group so that, just because he may not have specifically been aware of these products that we talked about until 1966, does not mean he did not have expertise to talk about the safety and efficacy of bioflavonoids on October 9, 1962.

The COURT. We will agree that he had expertise as to the general subject in 1962, but, by his own admission, he never even heard of these drugs in 1962, so he could not have any knowledge of them in 1962.

The WITNESS. Yes, sir.

The COURT. Is that right?

The WITNESS. Yes, sir.

[103] The COURT. But he did have actual knowledge of these drugs at the beginning of 1966.

The WITNESS. Yes, sir.

The COURT. All right. Now, let's take it from there.

By Mr. HOFFMAN:

Q. Dr. Spaet, you said that you discussed bioflavonoids generally around 1962 with other experts?

A. Yes, sir.

Q. And you testified that there were possibly as many as ten, is that correct?

A. Experts, yes.

Q. Experts?

A. Yes.

Q. Can you name ten?

A. Can I name ten experts?

Q. With whom you discussed the safety or efficacy of bioflavonoids generally around 1962?

A. No, I could not name the actual individuals with whom I discussed it. That is an estimate.

Q. Can you name one?

A. One person with whom I discussed it?

Q. One expert of those ten.

The COURT. One doctor in your field.

The WITNESS. Not under oath, certainly not.

[104] By Mr. HOFFMAN:

Q. Could you specify under oath where such—one such conversation took place, in fact, not your speculation, but where it took place and in what circumstances?

A. I would not do that unless I saw fit to record it, because I have no way of referring back to any kind of accurate statement as to such conversation.

Q. So, then, there is no evidence that any such conversation actually took place, is that correct?

The COURT. No, that is not correct. We have his evidence that it took place, so there is some.

By Mr. HOFFMAN:

Q. But you cannot tell us where it took place or exactly when or with whom?

The COURT. He has agreed that he cannot name the people or the time or the place, but he still says he had the conversation, so there is some evidence.

Mr. HOFFMAN. Your Honor, we would move to strike that evidence.

The COURT. Motion is denied. It goes to the weight of it.

By Mr. HOFFMAN:

Q. Doctor, you have testified that you are a hematologist; is that correct?

A. Yes.

[105] Q. And, I believe, you also testified that the subject of hematology deals with blood disorders; is that correct?

A. Yes, but not only—

Q. Are hematologists usually or commonly concerned with blood vessel abnormalities?

A. Some are.

Q. Are you?

A. I am.

Q. Doctor, I believe you have the labeling for these products in front of you?

A. I do.

The COURT. Let me have a copy of it so we both can read.

Mr. HOFFMAN. This is attached to the request for admissions.

The COURT. All right, whatever exhibit it is in—Government's request for admissions?

Mr. HOFFMAN. No, the defendant's, Your Honor—I am sorry—the plaintiff's.

The COURT. All right. Request for admissions, all right. Which one are you referring to?

Mr. HOFFMAN. The one with Exhibits A through K.

The COURT. All right, I have it here.

By Mr. HOFFMAN:

Q. Dr. Spaet, I direct your attention to Exhibit A, [106] which——

The COURT. That is the one that has a picture on it?

Mr. HOFFMAN. That is the one that has pictures of what looks like parts of a box.

The COURT. C, B, T, and so forth?

Mr. HOFFMAN. That is right.

The COURT. All right.

By Mr. HOFFMAN:

Q. Dr. Spaet, would you please direct the Court's attention and mind to the place on Exhibit A, where the product is recommended for any one of the underlying conditions for which, you testified, you thought the product was unsafe because ineffective.

A. That is——

Mr. EPSTEIN. I am raising an objection, Your Honor, to that question on the grounds that the documents to which we referred and the answers to which Dr. Spaet responded were to all of the statements in it, and we did not specifically come to any one exhibit to ask for his answer. The statements are contained in more than one.

The COURT. Objection is overruled.

I asked the Doctor myself, and I understood him to say so, if the labeling that the company put out for the information of the doctor, in his opinion, would indicate to [107] the doctor that this capsule would do something for a specific ailment, and you went through several of them, and he said that the label so stated. Now, I think he is entitled to make him point out in the label where it refers to stopping bleeding from abortions. That is one of your questions.

Mr. EPSTEIN. I have no objection if he asks the question that way, but that is not what he did, Your Honor.

The COURT. What did he do?

Mr. EPSTEIN. He asked him if——

Mr. HOFFMAN. This is cross, Mr. Epstein.

The COURT. Objection is overruled.

Go ahead. I think it is a fair question.



The WITNESS. Your Honor, may I have some clarification—

The COURT. Sure.

The WITNESS (continuing). As to what constitutes a label? Is a label merely what is stuck on the bottle? Is a label—

Mr. HOFFMAN. We are talking about Exhibit A.

The COURT. It is in Exhibit A. That is what is given to the doctor.

The WITNESS (continuing). Because there are other material—

The COURT. Everything in Exhibit A is what he says was given to the doctor.

Mr. HOFFMAN. We are not saying that was all, [108] Your Honor, but I started with Exhibit A, and I would like Dr. Spaet to testify.

The COURT. That is the label, isn't it?

All right. Now, ask him the question. You want to know about Exhibit A. What do you want to know?

By Mr. HOFFMAN:

Q. I would like to know, Doctor, where in Exhibit A the product Duo-C.V.P. with Vitamin K, or any of the other labels that are reproduced on that sheet—

A. It is not to be found on that sheet.

Q. Not to be found on that sheet?

A. That is right.

Q. Now, would you kindly point out on Exhibit B where it is recommended that the product be used to cure the underlying condition which produces, or, in conjunction with which may be found abnormal capillary fragility and permeability.

A. It is not offered to cure the underlying condition. It is offered to cure the manifestation.

Mr. HOFFMAN. Thank you.

The COURT. On what page is it offered to do that? Whereabouts?

The WITNESS. This is on Exhibit B, on the line that says "Indications".

Mr. HOFFMAN. We will accept that answer, Your [109] Honor.

The COURT. All right.

Now, let me see it, though. That is on B—Is that the first page of B or—

Mr. HOFFMAN. Yes, I believe it is, Your Honor.

The COURT. The one, at the top it is marked "1962-63", and so forth?

Mr. HOFFMAN. Yes.

The COURT. Where is this line that you are re-referring to, Doctor?

Mr. HOFFMAN. Your Honor, I think he is referring to the whole card, which is a single document and includes different columns, and so forth, and we are very satisfied with that answer and would like to move forward.

The COURT. You may be satisfied with it, but I want to see it.

Where is it?

Mr. EPSTEIN. Sorry, Your Honor, this is the wrong document.

The COURT. I've got the wrong document. No wonder I cannot find it. Give me the right document. This is request for admissions.

Mr. EPSTEIN. That is ours, Your Honor.

The COURT. You do not want that one?

Mr. EPSTEIN. No, we have the other one.

[110] Mr. HOFFMAN. Here is another set of the tabs.

The COURT. All right. We've got so many of them here. Here it is. This is the one, I assume. Is this it?

Mr. EPSTEIN. That is exactly it, Your Honor.

The COURT. All right. Now we are back to B.

Mr. EPSTEIN. Excuse me.

The COURT. All right.

Now, you say it is the first line. Where, Doctor, that you just said it indicates——

The WITNESS. Indication, the whole area that is covered by indications.

The COURT. Where is that?

The WITNESS. It is on the right hand side of the card.

The COURT. Oh, "Indications, Dosage, Adult".

The WITNESS. Are we looking at the same sheet?

The COURT. I hope we are.

The WITNESS. It says "Exhibit B."

Mr. EPSTEIN. Your Honor, it is on the page behind the tab that says "B" on it. It is the page directly following the——

The COURT. The second page, where it says "Indications of Dosage continued"?

The WITNESS. The second page?

Mr. HOFFMAN. What is the second page?

[111] The WITNESS. There is no second page.

Mr. HOFFMAN. Right here.

The COURT. I've got Exhibit B. There is page 1, Exhibit B, page 2.

The WITNESS. Okay.

The COURT. Have you got that?

Mr. HOFFMAN. I believe so, Your Honor. Each page appears to be a picture of a card similar to the one——

The COURT. That is right.

Mr. HOFFMAN (continuing). Setting on the clerk's desk.

The COURT. And it says, "Capillary fragility, Duo-C.V.P." Now, I don't see—On page 2, it doesn't say anything about indications and dosage. It does——

The WITNESS. On page 1, it does.

The COURT. Yes.

Mr. HOFFMAN. Are we looking at the same——

The COURT. Yes. Have we got the same?

Mr. HOFFMAN. Yes, we are, Your Honor.

The COURT. All right.

What line on that page do you want me to read?

Mr. HOFFMAN. Your Honor, in the right hand column, which begins "C.V.P. and Duo-C.V.P." parallel——

The COURT. Yes.

Mr. HOFFMAN. Okay. The first indented subparagraph.

[112] The COURT. All right.

Mr. HOFFMAN. Help to maintain normal capillary permeability, and it goes on——

The COURT. All right.

Mr. HOFFMAN. Now, I believe Dr. Spaet has testified that, in his opinion, this labelling represents the products involved, not for the underlying condition in conjunction with which abnormal capillary permeability and fragility are found, but, rather, for what the Doctor termed the manifestation. Perhaps the symptom would be a layman's word.

The COURT. All right.

By Mr. HOFFMAN:

Q. Is that correct, Doctor?

A. This is the way it is stated.

The COURT. All right.

By Mr. HOFFMAN:

Q. Doctor, can you think of any reason why a physician should not attempt, if, in his judgment, he so chooses, to treat both the underlying condition and what we have called the manifestation?

A. Well, I think that a physician should certainly try to do the combination of the two. However, when a drug is offered to treat a symptom and the symptom itself is what the physician sees, that may be all he does, if this is how he is indoctrinated.

[113] Q. That may be all he does, you say?

A. Yes.

Q. Is that all he does?

A. Frequently it is.

Q. In your judgment, is such a physician a competent physician?

The COURT. Objection——

The WITNESS. In this particular activity, no.

The COURT. Objection sustained. I am not going to let him pass on the competency of any other doctor.

By Mr. HOFFMAN:

Q. Dr. Spaet, can you direct the Court's attention and mine to any place in Exhibit B or, indeed, anywhere else in this set of ten exhibits, in which it is stated or suggested by implication that these products are the exclusive therapy to be used in any particular patient's case?

A. I think I can.

Q. Please do.

A. All right. It says the anti-hemorrhagic effect——

The COURT. What page are you reading on, Doctor?

The WITNESS. I am reading on page 2 of Exhibit C.

The COURT. Exhibit C, page 2. All right.

The WITNESS. That is right.

The COURT. All right.

[114] The WITNESS. It is the paragraph entitled, The Physiologic Effects of C.V.P. That is the entire section.

The COURT. All right, I see it, the left hand column. All right.

The WITNESS. Right.

It says: "Clinically, the anti-hemorrhagic effect of C.V.P. has been demonstrated in such bleeding conditions——" And there is a list, but I would like to emphasize the last term on the list. It says, "Hemorrhagic diatheses". Now, when this is

offered as a treatment of hemorrhagic diatheses, what the company is saying, in effect, is that anybody who bleeds from any reason should be treated with this agent, and no indication is given that there should be any other form of treatment. This is a treatment for hemorrhagic diatheses that is being offered. That includes hemophilia; it includes patients who have——

Mr. HOFFMAN. Excuse me, Dr. Spaet.

The WITNESS. This is the common understanding——

The COURT. Now, let him answer.

Mr. HOFFMAN. I would like to have that answer stricken as not responsive to the question.

The COURT. Let him answer.

The WITNESS. This is the common understanding as to what the physician means by hemorrhagic diatheses,——

The COURT. All right.

[115] The WITNESS (continuing). And I would like to make it perfectly clear that when the term "hemorrhagic diatheses" is used, this is a blanket covering any abnormal bleeding condition.

The COURT. That is what you understand the word to mean and what doctors understand it to mean?

The WITNESS. That is right.

Mr. HOFFMAN. But that was not the question, Dr. Spaet, and I move to strike the answer as not responsive.

The WITNESS. The question is, this is being offered to treat hemorrhagic diatheses and anything that is left out in any previous statement of what it is offered to treat is included in the term "hemorrhagic diatheses".

By Mr. HOFFMAN:

Q. Dr. Spaet, the question was: where, in that paragraph does it say, expressly or by implication, that C.V.P. is to be used or should be used as the exclusive therapy for hemorrhagic diatheses or any of the other underlying conditions that are listed in the preceding lines?

The COURT. He said that is what it means to him right there.

By Mr. HOFFMAN:

Q. Is that the way you interpret it, Dr. Spaet?

The COURT. That is what he said.

The WITNESS. That is the way I interpret the [116] company to mean it.

By Mr. HOFFMAN:

Q. No. The question is——

A. If the company offered penicillin, it would not say——

Q. Excuse me, Doctor.

A. (continuing). The giving of the penicillin would give oxygen.

Q. Doctor, wait a minute. You are not answering my question.

A. I understand——

Q. I respectfully ask you to wait until a question is asked.

The COURT. He has answered it. Go ahead. Next question. You may not agree with his answer, but that is what he says it does. To him, it means that.

By Mr. HOFFMAN:

Q. Dr. Spaet, I believe your answer was that this is what you thought the company meant. The question was: Is that what you understood it to mean?

A. That is what I understood it to mean, yes.

Q. So, in effect, you would be taken in by this?

Mr. EPSTEIN. Your Honor, I object to the form of the question.

The COURT. Objection is overruled.

[117] Let's get on with this case. The Doctor will take care of himself.

The WITNESS. Shall I answer the question as to whether I would be taken in?

The COURT. If you want to.

By Mr. HOFFMAN:

Q. I think I would like to have an answer, yes.

A. No, I wouldn't.

The COURT. He would not believe it is what he is going to tell you. Next question. Even though it said it—Isn't that right, Doctor?

The WITNESS. That is right.

The COURT. But he says others would.

Now, let's get on with the case.

By Mr. HOFFMAN:

Q. Would other doctors believe it?

A. Pardon me?

Q. Would other doctors believe it?

A. Absolutely. They do.

Q. On what do you base that statement?

A. On the fact that they publish papers on it.

Q. So you disagree with those papers?

A. Yes, absolutely.

The COURT. Now, wait a minute. You say other doctors published papers that these bioflavonoids did do what [118] this company says it does?

The WITNESS. That it stops bleeding.

The COURT. I say, other doctors published papers to that effect?

The WITNESS. That is right.

The COURT. Well, that is the other doctors' opinion, then, isn't it?

The WITNESS. That is right.

The COURT. He is entitled to his opinion, the same as you are entitled to yours.

The WITNESS. Quite so. I am just pointing out that he did, indeed, believe it.

The COURT. That would not follow that he was taken in. The other doctor might be right and he might be wrong.

Now, I understand that some doctors do agree that it does the very thing that you say it will not do.

The WITNESS. That is right, they do.

The COURT. So we now have it in the record. It is not a consensus.

Mr. HOFFMAN. We have in the record, not only from Dr. Spaet, but a stipulation from the plaintiff, that there is not a consensus in favor of the products' effectiveness.

[130] . . .

By Mr. HOFFMAN:

Q. Dr. Spaet, are you familiar with the specific component ingredients of the plaintiff's C.V.P. bioflavonoid products?

A. Do you mean biochemically?

Q. Yes.

A. No, I am not.

Q. They are in evidence in this case. Is it your understanding that the plaintiff's bioflavonoid products contain the identical

constituents with the other bioflavonoid products which were reviewed by your panel?

[131] A. It is my understanding that there is variation from one corporation to another.

Q. I would direct—Let me ask you a question, Dr. Spaet: Is it valid to equate all bioflavonoids with respect to efficacy for all conditions of use that are represented on the label? What would your answer be to that question?

A. My answer would be that until efficacy is demonstrated for any material, there is no efficacy for it.

Mr. HOFFMAN. I do not believe that is a responsive answer, Your Honor. I would move to have it stricken.

The COURT. Just ask him the next question. There is no use to strike it. It is in there.

By Mr. HOFFMAN:

Q. I would like to ask for an answer to this question: Is it valid to equate all bioflavonoids with respect to efficacy?

The COURT. In other words, do they all use—do you—

Mr. HOFFMAN. Are they all alike?

The COURT. Do you equate them all the same?

The WITNESS. I have no idea whether it is valid or not to equate them or not at this point.

The COURT. All right.

The WITNESS. I do not think the evidence is in that indicates whether such a statement can be answered.

[132] Mr. HOFFMAN. Your Honor—

The COURT. The answer is, if they do have different constituents, they are not necessarily going to have the same end results; isn't that correct?

The WITNESS. That is quite possible, but that doesn't mean that just because one is different from another, it is going to develop a sudden miraculous efficacy.

The COURT. No, and it does not mean that it won't, either, does it?

The WITNESS. No, it doesn't.

The COURT. What?

The WITNESS. That is true.

The COURT. So, therefore, you cannot answer it. Without knowing the constituents, you cannot give an answer.

The WITNESS. I thought that is what I said.



The COURT. That is all you've got to say. These questions are not hard to answer.

Mr. HOFFMAN. Your Honor, I would like to direct the witness's attention to pages 51 and 52.

The COURT. He has answered. He says, without knowing the specific contents, he does not know what the end result will be.

Mr. HOFFMAN. Your Honor, this is in the nature of impeaching that answer in that he testified on deposition, when asked that precise question, "Is it valid to equate all [133] bioflavonoids with respect to efficacy for all conditions of use that are represented in the labelling?"

"A. Probably not.

"Q. Would you explain that?"

The COURT. That is the same answer he made now, only—

Mr. HOFFMAN. Page 52.

The COURT. He said definitely not, now; he said there, "Probably not." That is not impeaching.

Mr. HOFFMAN. If that is the same answer, fine. I understood him to say he could not answer.

The COURT. Why isn't it the same answer? He says "definitely not" and "probably not".

Next question.

Mr. HOFFMAN. Okay.

The COURT. It just goes to the degree of it.

Mr. HOFFMAN. Would you indulge me a moment, please, sir?

The COURT. Yes, sir.

By Mr. HOFFMAN:

Q. Dr. Spaet, do you know of any reports in scientific literature, or any reports of physicians reporting on their patients' reactions, that show or suggest that any of the plaintiff's products involved in this case are toxic, per se, that is, do they affirmatively, in themselves, cause harm?

[134] A. I am unaware of any reports in the literature. I would like to say, however—

Mr. EPSTEIN. Objection.

The COURT. Objection is overruled.

What is your objection?

Mr. EPSTEIN. My objection is that that is what we did stipulate to this morning, that they were not pharmacologically toxic—

The COURT. You said they were not——

Mr. EPSTEIN (continuing). So, apparently, the confusion in counsel's mind as to what the stipulation was.

By Mr. Hoffman:

[137] Q. Dr. Spaet, are you familiar with the term "drug of choice"?

A. I am.

Q. Could you tell us what it means?

A. It means the drug that is most efficacious in treating a specific condition.

Q. Is it your view, Dr. Spaet, that any drug, other than the drug of choice, as you defined it, is an unsafe drug?

The COURT. Do we get any place with that?

Mr. HOFFMAN. I think we do, Your Honor.

The COURT. All right, answer it, Doctor.

Mr. HOFFMAN. We would like to have it in.

The WITNESS. I think it is a relative matter. The farther you get from the drug of choice, the less safe is the drug that you are using. It is sometimes—Well, you keep climbing until you reach a threshold, and then, finally, you are over it and you say, blank, it is unsafe, but it is less safe to use the drug that is not the drug of choice than it is to use the drug of choice.

The COURT. To really clarify this matter and to really muddy the waters, there are doctors who think aspirin is unsafe, don't they?

The WITNESS. I am one of them.

The COURT. All right. There are millions of doctors who think they are safe, and it is probably the most [138] commonly used drug for the most widely known number of ailments in existence, isn't it?

The WITNESS. Yes, sir.

The COURT. So, therefore, because good competent doctors like you, and I am serious by putting you in it, thinks it is unsafe, doesn't make it unsafe at all, does it? A perfect example—I am a living example of 68 years, and I've probably had thousands of aspirin.

The WITNESS. But Russian roulette, by the same token——

The COURT. I know.

The WITNESS (continuing). Can also be safe.

The COURT. I would hardly, Doctor—you are now reducing your opinion to almost a ridiculous state to put an aspirin, use of aspirin, in a class with Russian roulette. You do not mean that.

The WITNESS. I mean it just has more chambers.

The COURT. Do you mean it is equally as dangerous as playing Russian roulette?

The WITNESS. No——

The COURT. Well, I would hardly think it would be.

The WITNESS (continuing). But I have known people who have died from bleeding as a result of aspirin.

The COURT. For every one that you have known who [139] died from bleeding, other doctors can name ten thousand that have been relieved of an awful lot of pain, couldn't you?

The WITNESS. Oh, yes.

The COURT. What?

The WITNESS. I use it myself.

The COURT. I thought you did.

I mean I understand the situation, but just, per se, say something is unsafe because one man does not make it that way—I know one thing that is unsafe, and that is certain poisons you take, it is conclusive, isn't it?

The WITNESS. Oh, yes.

The COURT. You just do not make it if you drink it. That is what I call strictly unsafe.

Go ahead.

All right, go ahead.

By Mr. HOFFMAN:

Q. Dr. Spaet, what is the drug of choice, in your expert opinion, for abnormal capillary fragility and permeability?

A. It depends on what the underlying conditions is that is causing it.

The COURT. Again, we are getting back. The doctor wants to get away, and I am happy to hear him, but his drug of choice certainly would not be aspirin, but he would never convince me that aspirin was, per se, unsafe.

[140] Mr. HOFFMAN. No, I am trying to get back to this particular product, Your Honor.

The COURT. All right, let's get to the issue.

By Mr. HOFFMAN:

Q. Not for the underlying condition, what is the drug of choice, in your opinion, for abnormal capillary fragility and permeability?

A. I would like to point out that abnormal fragility and permeability is a completely different proposition. The term is misused. Let's say fragility, where they rupture more easily, that the drug of choice depends on why the patient has it. If the patient has scurvy, the drug of choice is vitamin C; if the patient has a condition in which he does not have any blood platelet, it is called thrombocytopeniaperia—if you are going to give a drug, if you are not going to take out his spleen, then you will give him prednis or one of the steroids. But the point is that there is no over-all answer that answers this question as to the drug of choice for any one of them. You have to find out why the patient has it and treat him appropriately.

Q. With all respect, Doctor, I am not asking for the drug of choice for the underlying condition or the root cause of that condition, but for the condition itself of abnormal capillary permeability and fragility. Is there a drug of choice, in your expert opinion?

[141] A. I think that it is a non-question.

Q. Well, I submit, it is a question.

The COURT. He has answered it. Go ahead. He says it depends.

Mr. HOFFMAN. Your Honor, I think the answer is non-responsive.

The COURT. All he is saying, Mr. Hoffman, is that you have to tell me what causes the condition and I will try to prescribe a drug that will relieve that condition, but if the cause is from five conditions, it may take five different drugs.

Isn't that what you are saying, Doctor?

The WITNESS. Or one of five.

The COURT. You know, I would make a good witness for you.

The WITNESS. Absolutely, sir.

The COURT. I mean, I think these questions are so obvious that I do not know why you people ask them.

Mr. HOFFMAN. I have no further questions of this witness.

The COURT. Let me just—and then to clarify the doctor—he wants to get away—Doctor, I understand, basically, your ex-

pertise and your opinion, based upon your honest findings and the opinions of your colleagues, is that this type of a drug, these bioflavonoids, as they are called, [142] are, for all practical purposes, like tap water, they are harmless, per se, and by being harmless, I mean, they do not do any good or any harm if you take them.

The WITNESS. Probably, sir.

The COURT. Since they leave the impression in the doctor's mind that they accomplish this specific result, they become unsafe because they deprive the doctor of the knowledge of having available a drug that will do that.

The WITNESS. Yes, sir.

The COURT. I mean, that summarizes it, isn't that correct?

The WITNESS. That is an accurate statement of my position. Your Honor.

The COURT. All right.

Now, I understand his position, and I will let you people argue it from there.

Do you want any further questions?

Mr. EPSTEIN. Excuse me just one moment, Your Honor, if I may.

The COURT. Certainly.

Mr. EPSTEIN. I have just a couple questions.

#### REDIRECT EXAMINATION

By Mr. EPSTEIN:

Q. Dr. Spaet, when you were taking about Exhibit C, if you have it there in front of you, you refer to it, I [143] will ask you to direct your attention, if you would, to Exhibit C and tell me if, beyond the paragraph which you were talking about on cross examination, are there any other representations in Exhibit C that talk about specific bleeding states or serious conditions for which this product is recommended. Just take your time and look through Exhibit C, if you would, sir.

A. Yes, there is a whole list of them.

Q. Would you tell me where they are and what they are, sir?

A. Yes. They begin on page 4—

The COURT. Page 4?

The WITNESS. That is right.

The COURT. All right, I've got 4.

The WITNESS (continuing). And it starts with habitual and threatened abortion; postpartum bleeding. It continues, epis-

taxis, otolaryngology, and tonsillectomy. It continues, purpura, ecchymosis; it continues, hypertension, and so on; it goes on and on.

By Mr. EPSTEIN:

Q. Doctor, as I understood you to describe it on cross examination, is it your opinion that when the drug is recommended in this literature for the conditions to which you have just indicated, that is the drug that is being recommended for those conditions?

[144] A. Yes. This is what I intended by labeling. Your Honor, the available literature that the physician has to him I consider essentially, basically, part of the label.

Q. Now, Dr. Spaet, on cross examination—

The COURT. Now, you would read this one, first two statements on there, if I were reading them, the first statement just says, "Three out of four habitual aborters delivered healthy babies." That could be a fact. I would not deny it, but that would not have anything to do with this pill, would it?

The WITNESS. No. That is the whole point.

The COURT. That is surplusage.

The WITNESS. Yes.

The COURT. Now, the second thing—So that would not fool any doctor to say three out of four habitual aborters deliver healthy babies?

The WITNESS. Would that it were so.

The COURT. I know, but that is what it says, "Two out of every three threatened aborters were enabled, —" Now, this is positive—"on C.V.P. treatment, to complete gestation and deliver live, healthy babies."

Well, it might be inferred that they would not have delivered healthy babies if they did not take C.V.P., but I do not think that would fool him that that helps you deliver healthy babies, would it?

[145] The WITNESS. Well, the implication is that if you are threatening abortion—

The COURT. What it comes down to is the last statement, where they say their findings show that there was a decrease in postpartum bleeding in the series of treated patients, as compared with non-treated patients.

Now, to me, that would read clearly that it, at least, had something to do with slowing down or curtailing postpartum bleedings, wouldn't it?

The WITNESS. That is the claim.

The COURT. That is the claim, and you say it has no effect on that?

The WITNESS. That is right, sir.

The COURT. All right.

I just wanted to get the statement. The first two, I think, is surplusage in there. Certainly, these pills have nothing to do with delivering babies.

The WITNESS. But, Your Honor, if you were an obstetrician, wouldn't you interpret this as a treatment, per se, for threatened and repeated abortions?

The COURT. No. If I were a very good doctor, I think I would read that if I had a bleeding patient, it might slow it down some, but I would not think it would cause me, the next time my patient got pregnant, she would or would not have a baby. I mean that is all it says there. But I would [146] certainly have to read it, that it would curtail bleeding.

The WITNESS. Yes.

The COURT. All right.

Go ahead.

By Mr. EPSTEIN:

Q. Well, Dr. Spaet, in talking about the papers, literature, that you have reviewed, are any of the other papers that you have reviewed demonstrate the proof of efficacy of these bioflavonoid products?

A. No, they have not.

Q. Have you read anything in the literature that proves the efficacy of the plaintiff's bioflavonoid products?

A. No, I haven't.

Q. In the course of your teaching duties, are you familiar with the current textbooks that are in use in the medical schools on the subject of hematology?

A. Yes. It is our policy, the policy of our department, to get all the latest textbooks, standard or unstandard, so that we have a complete collection of them.

Q. Do any of the now current textbooks that are being used in the medical schools, and most particularly on the subject of hematology, mention the bioflavonoids generally or these plaintiff's bioflavonoid products specifically as efficacious therapy in the bleeding states that we have discussed this morning?

[147] A. They do not.

The COURT. Do any of these medical journals or teachings say that they are harmful, the use of them?

The WITNESS. If I am not mistaken, Your Honor, the term does not appear in them.

The COURT. It means that they ignore it?

The WITNESS. Yes.

The COURT. They do not even mention it either way?

The WITNESS. That is right, sir.

The COURT. That leaves a big void. But they definitely, none of them, go to the trouble of saying—that warn the doctor in your field, stay away from these bioflavonoids because they cause a harmful effect?

The WITNESS. No, Your Honor, but on the other hand—

The COURT. If the doctors thought they did, why wouldn't they say so in their journal—

The WITNESS. Well, because—

The COURT (continuing). Even though this pharmaceutical house is working a fraud on the doctor, why don't the medical societies speak up like big people and say, "Our experience has convinced us that they are harmful; stay away from them"?

The WITNESS. Well, I think that the standard textbook has a different mission, and the standard textbook [148] tells the young man or the physician who is not familiar with the field what is new and what is good in it, and it does not have to go about—

The COURT. It does not warn him of the bad?

The WITNESS. There are so many bad possible things that you could fill the book with it.

The COURT. All right. I understand. You just say it only teaches modern medicine and overlooks what not to do.

The WITNESS. That is right, yes, sir.

By Mr. EPSTEIN:

Q. Doctor, on that subject and in connection with some of Judge Lewis's questions, when we are talking about harmful, I am asking you, is pharmacological toxicity, or the pharmacological adverse reaction, the same as the issue of safety as you are using safety in describing the modality of using these plaintiff's products to treat the condition?

Mr. HOFFMAN. Object, Your Honor.

The COURT. He answered it, and I have summarized it for him,



and he has told me very clearly whether he makes it synonymous with it, even though it is harmless——

Mr. EPSTEIN. Okay.

The COURT (continuing). If it causes a doctor not to do what he might otherwise do, it then becomes harmful. That is his theory.

[149] By Mr. EPSTEIN:

Q. Dr. Spaet, during the course of the deliberation of the panel on hematology and drug efficacy study that you were a member of for the NAS NRC, was there general discussion among the panel members, or was there consideration of the uses of bioflavonoids in the treatment of bleeding states in man?

A. There was.

Q. During the course of that consideration, or the deliberations that you had, did you find any evidence of the efficacy for any bleeding states in man of these bioflavonoid products?

A. We did not.

Q. Or of the plaintiff's bioflavonoid products in particular?

A. We did not.

Q. When you say "we", you mean yourself and the rest of the panel members?

A. The remainder of the panel, I think that in retrospect now, I could talk about the panelists as other experts in the area with whom I specifically discussed these bioflavonoids.

Q. Would you give us their names, if you remember them, Dr. Spaet?

A. I can, some of them.

The COURT. I will concede he discussed it with [150] all the members of the panel.

\* \* \* \* \*

#### RECROSS EXAMINATION

By Mr. HOFFMAN:

\* \* \* \* \*

[151] \* \* \*

Dr. Spaet, [152] on Exhibit C, page 4, to which Mr. Epstein referred you, am I correct in my recollection that you began reading about a third or so of the way down the page, the phrase beginning "Habitual and threatened abortion"?

A. Yes.

Q. And was it your testimony that you thought that was labelling that suggested that the products involved were being recommended for habitual and threatened abortion, and so forth?

A. That is right.

Q. I wonder if you would please read from the top of that page so as to put that last clause of the sentence in context, beginning "To help correct"?

A. "To help correct"—Do you want me to read it aloud?

The COURT. He does not need to read it. I can see it right here.

Mr. HOFFMAN. Fine, then.

The WITNESS. Okay.

Mr. HOFFMAN. I just wanted to direct the Court's attention to the fact that Dr. Spaet's testimony was reading part of a sentence out of context.

\* \* \* \* \*

[154]

#### REDIRECT EXAMINATION

By Mr. EPSTEIN.

Q. Doctor, did you tell us when you first started the survey of the literature concerning bioflavonoids?

A. It was in the early 1950's, that is that the bioflavonoids were caught up in my literature search net.

Q. And you saw the literature at that time?

A. Oh, yes.

Q. And reviewed it?

A. Yes. Maybe 1949.

The COURT. Do I understand, so that there will not be any misunderstanding, these bioflavonoids, not necessarily this one, because I think the record here reflects to 1962, as far as this information came out, but were comparable products in this general field, with, maybe, some minor additions, you know, to make it a little different, like Bayer's aspirin and somebody else's aspirin, have they been in common use in the medical field since when, 1949 or—

The WITNESS. About that, somewhere around there.

\* \* \* \* \*

[159] [Milton Corn was called as a witness, and having been first duly sworn, was examined and testified as follows:]

## DIRECT EXAMINATION

By Mr. EPSTEIN:

[165] \* \* \*

Q. Coming back specifically to the plaintiff's product, C.V.P. capsules, Doctor, is it your opinion that the administration of C.V.P. capsules to a patient who has the condition or is suffering from postpartum bleeding, is a safe modality for the treatment of that condition?

A. I don't believe it is.

Q. Why not?

The COURT. I do not want to get into this unless I have to, but isn't the only issue we are determining whether this was a new drug introduced in the market in 1962 and whether, as a result of it, it is covered by the grandfather clause? Isn't that the only thing we are going to decide here on this case?

Mr. EPSTEIN. Yes, but, Your Honor—

[177] \* \* \*

By Mr. EPSTEIN:

Q. Dr. Corn, on October 9, 1962, did you know about bioflavonoids?

A. Yes.

Q. On October 9, 1962, did you have an opinion about the use of bioflavonoids for the treatment of bleeding conditions?

[178-199] Mr. HOFFMAN. Objection, Your Honor.

The COURT. Objection is overruled.

I mean the record is clear that you've got opinions on both sides, so we will add his for one more.

Mr. HOFFMAN. He is not talking about the product in this case, Your Honor.

The COURT. No, but we are talking about—We are going to put the product in this category. He is talking about general.

The WITNESS. Yes.

The COURT. Go ahead.

[200] By Mr. EPSTEIN:

Q. What was that opinion, Dr. Corn?

A. That it was medically ineffective and had no indication of which I was aware of for use in sick people.

The COURT. In other words, you go farther than the other. You say it has no medicinal value for any purpose period.

The WITNESS. That is my opinion.

The COURT. All right.

By Mr. EPSTEIN:

Q. Dr. Corn, coming to today, is that your opinion today also about the bioflavonoids?

A. Yes, it is.

Q. Is that opinion shared by your colleagues?

A. Insofar as I know.

Q. And is the opinion that you specified to me that you held on October 9, 1962, to the best of your recollection, was that opinion also held by your colleagues then?

A. Yes, as far as I know.

Q. Doctor, coming to the specific products of the plaintiff's drugs, are C.V.P. CAPSULES a bioflavonoid product?

A. Yes, they can be.

The COURT. I thought it was conceded they were.

Mr. EPSTEIN. Yes.

[211] \* \* \*

Mr. EPSTEIN. Then to that extent I would then ask him the same question is it a safe modality to give C.V.P. capsules to a patient who would be suffering from postpartum bleeding, and I ask for your answer.

The WITNESS. No, I don't think it is.

The COURT. Tell me, doctor, to get—to get to the nub of it—Dr. Spaet told me—Why isn't it safe? Why isn't it safe? He is asking you if it is safe to give it to them. Medically why isn't it safe?

The WITNESS. The same type of reasoning that was brought out this morning.

The COURT. Yours is predicated on the same basis—

The WITNESS. Yes.

The COURT (continuing). Because it in your opinion keeps a doctor from giving him something that is better?

The WITNESS. That's right.

The COURT. It is not unsafe to give a bleeder a glass of water, is it?

The WITNESS. No, it isn't.

The COURT. Nor an aspirin, is it?

The WITNESS. Not usually.

[212] The COURT. All right. So now I am not saying that a bleeder you ordinarily wouldn't give aspirin—

The WITNESS. Right.

The COURT (continuing). But you wouldn't say it is harmful or unsafe.

So let's get to the nub of this case. We are not getting anyplace.

I understand your argument. You don't need any more evidence to convince me of your argument. Whether I will buy it or not is another story. And their argument is that since this, conceding it is harmless, like water, since the doctor is taken in by believing that it's going to give some positive effect, it becomes harmful because it keeps the doctor from giving what you say he ought to give them. Isn't that right?

The WITNESS. That's right.

The COURT. All right. I understand your logic.

[214] . . .

By Mr. EPSTEIN:

Q. Doctor, I want to ask, if I may quote to you the following statement and ask you whether you agree or disagree with it:

"The high hopes once held out for the flavonoids as important metabolites have not materialized. Instead present knowledge indicates that while they possess mild pharmacological properties under certain conditions the flavonoids have no known nutritional functions. They cannot—"

The COURT. No, known what?

[215] Mr. EPSTEIN. No known nutritional functions.

The COURT. We are getting in the class with Post Toasties now, aren't we?

Mr. EPSTEIN. I hope not, your Honor.

The COURT. I read something about they have no nutritional value too.

Mr. EPSTEIN. That will be a new one before you at some later time.

"They cannot be regarded as essential nutrients. Those workers who claim therapeutic value for the flavonoids have not

supported their claims with data obtained from well-controlled clinical studies. Until such studies are made, it must be concluded that the flavonoids are of little or no value in the treatment of disease."

By Mr. EPSTEIN:

Q. Do you agree or disagree—I'm sorry—If I may, doctor, I will put it before you.

A. Well, I read what you read.

Q. And ask you again, renewing my question, do you agree or disagree with that statement?

A. I agree.

Mr. HOFFMAN. Mr. Epstein, are you offering that statement that you just read in as proof in itself of the matter?

The COURT. No. It is evidence of what that [216] author said. That doesn't make it a fact. That is his opinion.

Mr. EPSTEIN. And I am offering it as the opinion of Dr. Corn which he just stated the view contained therein.

The COURT. It is Dr. Corn's opinion insofar as the part he agrees with.

Mr. EPSTEIN. Yes, sir.

By Mr. EPSTEIN:

Q. Now Dr. Corn, is the statement that is—Yes, sir.

A. Well, I agree with everything except the fact that high hopes were once held. I don't know who held the high hopes.

The COURT. I would agree with that. If they held high hopes I would want to know what they were and when they dropped.

The WITNESS. They weren't mine.

The COURT. What?

The WITNESS. They weren't mine.

The COURT. They must at one time because—

The WITNESS. Someone must have.

The COURT (continuing). According to this expert they had high promise for medicinal purpose; isn't that right?

The WITNESS. Yes.

[217] The COURT. The test ought to show what the negative responses were and that article doesn't prove much, does it? It is in generalities, isn't that correct, doctor? It just says the high hopes, it doesn't live up to high hopes. What does that mean?

Mr. EPSTEIN. Your Honor, since it is in evidence I didn't quote to him the whole thing. There is a four-page document.

What I asked the doctor's opinion on was the summary or in effect conclusion to this article.

The COURT. He said he read all of it but he doesn't agree with the first premise so that just drops it all.

I mean you have nullified it by a single statement. If his premise is wrong his conclusion is wrong. So he says the premise it had high hopes he cannot agree with it.

By Mr. EPSTEIN:

Q. But I do understand you to say, Dr. Corn, that except for that sentence you do concur with the statement?

Mr. HOFFMAN. Object to the leading question, your Honor.

The COURT. It doesn't make any difference.

Let's get on with it.

He agrees with it.

The WITNESS. I agree with that, and I simply don't know whose high hopes these were, but the remainder of [218] the statement insofar as it refers to the actual value and the data pertaining to flavonoids I agree with completely.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration of the plaintiff's C.V.P. capsules to a patient who is suffering from hypertension would be a safe modality for the treatment of that condition?

Mr. HOFFMAN. Objection, your Honor. The same grounds as before.

The WITNESS. No.

The COURT. Let it in. His answer is going to be no.

The WITNESS. Yes.

No.

By Mr. EPSTEIN:

Q. Would you tell us why, doctor? Would you tell us why it would not be a safe modality, Dr. Corn?

The COURT. He says that all of his safety is predicated on the fact that it keeps the person from getting a safe or better product.

The WITNESS. That is quite right. Hypertension can kill people, and I think the doctor taking care of hypertension has considerable responsibility to treat it just as intelligently and

as quickly as he can, and I think that any time loss or waste, whether it is two months, two weeks or [219] two minutes on an inefficient or inefficacious remedy is not only valueless but prejudicial to the health of the patient.

The COURT. Let me ask you this, doctor.

The WITNESS. Yes.

The COURT. Are placebos valueless to the medical profession?

The WITNESS. No. They are of considerable value if used correctly.

The COURT. I say that many doctors think they are necessary, don't they?

The WITNESS. Yes.

The COURT. And a placebo is apparently in the category with this pill, according to you. It has neither nutritional nor medicinal value but it doesn't harm much, so it is in the category of the placebo. Is that right?

The WITNESS. It is except for the intent in its use.

The COURT. You give placebos for a lot of things, don't you?

The WITNESS. Yes. \* \* \*

[221] \* \* \*

By Mr. EPSTEIN:

Q. I will ask you, doctor, if your opinion that you [222] have just enumerated that you just discussed with me as to the bio-flavonoids today, was that your opinion, did you hold the same opinion on October 9, 1962?

A. Well, yes, I am sure that it would have been.

The COURT. I take it so whatever it is germane, from your standpoint, doctor, they never were worth anything.

The WITNESS. That's right, Judge. That is exactly my feeling.

The COURT. Now I will go further than you did.

Mr. EPSTEIN. Fine, sir.

The COURT. You never recognized them as being medically worth a bottle.

The WITNESS. That's right.

Mr. EPSTEIN. Fine.

I have no further questions on direct, sir.

The COURT. All right.

Mr. HOFFMAN. Your Honor, I hope to be much briefer than we were with Dr. Spaet.



## CROSS EXAMINATION

By Mr. HOFFMAN:

Q. Dr. Corn, I believe you testified that you were unacquainted with the plaintiff's C.V.P. products involved in this case until five or six months ago; is that correct?

A. Yes, Mr. Hoffman.

Q. And you testified that in October of 1962 [223] you were familiar with other bioflavonoids products, is that correct?

A. Bioflavonoids in general.

Q. Could you enumerate the ones with which you were familiar?

A. No, and this is the point that was brought up before. If in fact one is thinking about a class of compounds, it isn't necessarily—it doesn't necessarily mean that I know or even need to know every specific commercial source of such, and I am not sure—if that is what you're getting at.

Q. I am asking if you do know, if you can identify any particular, as you put it, commercial source of the product that you consider a bioflavonoid in the same class as plaintiff's C.V.P. product?

A. No, I cannot, and the reason being that all the information I had ever received or had in fact read about had left me with the opinion I expressed here today. Since I have never felt the need under any circumstances to use this on a patient it was never necessary for me to find out who was making it.

The COURT. Let me get at it this way, doctor.

Personally you have never used one?

The WITNESS. Never.

The COURT. You don't know of any doctor who has ever used any?

[224] The WITNESS. I personally have never met a physician who has used it.

The COURT. Therefore you obviously from experience could know nothing about it except what you read?—

The WITNESS. That is quite right.

The COURT. All right.

Does that answer all your questions?

Mr. HOFFMAN. Almost, your Honor.

The COURT. He knows very little about it. I will tell you.

By Mr. HOFFMAN:

Q. Do you know, can you tell us, what the ingredients are in C.V.P. capsules?

A. Well, I can read the label, as you did. It said it is a citrus of bioflavonoids——

Q. Compound?

A. Compound and it also contains a hundred milligrams of Vitamin C.

Q. Is it your understanding that all the products that you would consider in the bioflavonoid class contain citrus bioflavonoid compound.

A. No. Bioflavonoid compounds can be obtained from a variety of plants and fruits.

Q. So then you have no particular reason to think, is that correct, that the C.V.P. capsules do in fact have the [225] same ingredients as the products that you were familiar with in 1962?

The COURT. He says he is not familiar with any products. He is only familiar with the general subject matter that he has read. That is what the doctor said.

Mr. HOFFMAN. Let me reframe the question then.

The COURT. And he knows no doctor who has ever used one.

By Mr. HOFFMAN:

Q. What is your reason to think, Dr. Corn, that the ingredients of C.V.P. capsules are the same in relevant respect as these other bioflavonoids with which you were familiar in 1962?

A. Since I think it is a generalization of the class of bioflavonoids that they have such and such action or not such and such action, and I think someone who feels that he has some special subgroup of bioflavonoids compounds that can do something has in fact got the burden of demonstrating this. Simply saying, that you have citrus bioflavonoid compounds tells me neither one way nor the other, whether your compound is specifically different or similar to.

Q. In other words, you cannot tell, there may be a difference, you can't say that they are the same; is that correct?

The COURT. You are arguing with him now. He [226] has told me; what he knows about them.

Mr. HOFFMAN. I would like to get the witness to say whether or not he believes that all bioflavonoids are necessarily the same or whether differences among them might result in differences.

The COURT. He says they aren't the same. One comes from an orange, one comes from a lemon, one comes from a vegetable, plus other articles; isn't that right?

Mr. HOFFMAN. There may be differences. That is right.

The COURT. So they obviously couldn't be identical.

By Mr. HOFFMAN:

Q. Dr. Corn, have you ever considered a difference between water soluble by a flavonoid and insoluble by flavonoids?

A. Yes, I have considered it in the sense of thinking about it and have noticed the distinction in some standard pharmacology description of these agents.

Q. Do you know into which group C.V.P. capsules fall?

A. I know that there is a statement made by the makers that it falls under the water soluble group.

Q. Can you tell us whether any of the bioflavonoid products with which you were familiar in 1962 also fell into [227] that group?

A. I cannot.

Q. Dr. Corn, directing your attention to Defendant's Exhibit D, which is the article—

A. Yes.

Q. What was the date—no—this is the one Dr.—Mr. Epstein gave you?

A. Yes.

Q. What is the date on that article?

A. 1957.

Q. Do you know whether or not any studies on bioflavonoids have been done since that article?

A. Quite a large number.

The COURT. What was the answer?

The WITNESS. Yes, a number of studies have since 1957.

The COURT. He didn't ask you. There must be a reason. What do they show?

Mr. HOFFMAN. We hope to get to that if the day holds out, your Honor.

The COURT. All right.

Mr. HOFFMAN. We don't think this witness is the vehicle.

The COURT. If he knows.

Do they hold the same position as this one, [228] these other studies that you have seen?

The WITNESS. No.

The COURT. What do they hold? What do they—what is the difference if you know?

The WITNESS. Yes. There is a variety of studies, many of them reports by people who feel that they used it in a group of patients and it helped some of them.

The COURT. All right. So there are some favorable subjects.

The WITNESS. There are some, yes.

The COURT. He recognizes that there are some that are favorable.

Go ahead.

But he has a right to his opinion.

By Mr. HOFFMAN:

Q. Dr. Corn, does that article, Exhibit D, deal with C.V.P. capsules or duo-C.V.P. specifically?

A. I don't believe so.

Q. Do you know, if you know, whether any of the later studies to which you refer, which you have just discussed with the Court, do deal with C.V.P. or duo-C.V.P. specifically?

A. Yes, some of them do.

Q. Dr. Corn, directing your attention to the stipulated exhibits, what has been called here the label, directing [229] your attention to Exhibit C, the fourth page of that exhibit—do you have it?

A. I think so. This is the picture?

Q. No. The fourth page. It is numbered four on the bottom. Keep going.

A. Oh, I see. Yes.

Mr. HOFFMAN. Excuse me a moment, your Honor.

Your Honor, I think that I prefer to withdraw this line of questioning.

The COURT. All right.

Mr. EPSTEIN. I'm sorry. I didn't hear what you said.

Mr. HOFFMAN. I said I prefer I think to withdraw this line of questioning and it will not be necessary to refer to the labels.

The COURT. All right.

Do you have any further questions?

Mr. HOFFMAN. No further questions, your Honor.

Mr. EPSTEIN. I have two questions I want to ask him, if your Honor please?

The COURT. All right.

## REDIRECT EXAMINATION

By Mr. EPSTEIN:

[231]

The COURT. All right.

[232] They have rested.

Do you have any rebuttal?

Mr. HOFFMAN. Yes, we do, your Honor.

The COURT. All right. Call the first witness.

Mr. HOFFMAN. Dr. Karpman, please.

Whereupon,

[Harold L. Karpman was called as a witness and, having been first duly sworn, was examined and testified as follows:]

Mr. HOFFMAN. Mark this as Plaintiff's Exhibit 5 for identification.

(Dr. Karpman's curriculum vitae was marked for identification as Plaintiff's Exhibit No. 5.)

## DIRECT EXAMINATION

By Mr. HOFFMAN:

Q. Doctor, would you please state your name and address for the record?

A. Harold L. Karpman, 465 North Roxbury Drive, Beverly Hills, California.

Q. What is your profession?

A. I am a physician.

Q. What position do you hold, doctor?

A. I am chief of the Peripheral Vascular Laboratories of the Cedars-Sinai Medical Center, assistant clinical professor of medicine, Southern California School of Medicine, [233] president-elect of the American Thermographic Society, fellow of the American College of Physicians, the American College of Cardiology, the American College of Chest Physicians, the International College of Angiology, the American College of Angiology.

Mr. EPSTEIN. Your Honor, we are willing to stipulate the curriculum vitae.

The COURT. He has a very extensive one.

I always wondered sometimes when these doctors belong to all these societies how they get any time to practice medicine.

Mr. HOFFMAN. They are too busy determining the consensus, your Honor.

The WITNESS. We work long hours like judges.

The COURT. What?

The WITNESS. We work long hours like judges.

The COURT. I see.

No, I'm just being facetious.

The Court rules the doctor is well qualified and he is an expert and may give an opinion in his field of medicine if he be advised.

Go ahead.

Mr. HOFFMAN. We move the admission of the curriculum vitae which is marked as Plaintiff's Exhibit 5.

The COURT. Let it be admitted.

[234] (Plaintiff's Exhibit No. 5, heretofore marked for identification, was received in evidence.)

By Mr. HOFFMAN:

Q. Doctor, are you affiliated with a major hospital? I believe you named one.

A. Yes.

Q. Could you repeat that?

A. I didn't name them. I am affiliated with Los Angeles County Hospital, Cedars-Sinai Medical Center, Saint Vincent's Hospital in Los Angeles.

The COURT. Do you consider those major hospitals?

A. Yes, they are very major hospitals.

Q. Are you acquainted with the C.V.P. products manufactured by the plaintiff in this case?

A. Yes, I am.

Q. Which ones?

A. Duo-C.V.P. primarily.

Q. Are you familiar with C.V.P.?

A. Yes.

Q. Could you tell us the circumstances in which you became familiar with it?

A. In 1957 during the course of my training I became involved in the study of the vascular diseases as well as cardiology and my interests in agents that would affect the [235] vascular problems started at that time.

Q. Have you used C.V.P.<sup>4</sup> or duo-C.V.P. in your practice?

A. Yes, I have.

Q. Do you now?

A. Yes.

Q. In the course of your studies have you had occasion to become familiar with the scientific literature in the field of bioflavonoids?

A. Yes.

Q. Have you become familiar with the scientific literature specifically on C.V.P. and duo-C.V.P.?

A. I am certain not all of the literature but a great deal of it.

Q. Have you discussed C.V.P. and duo-C.V.P. with other experts in the field?

A. Yes, I have.

Q. Can you give us some names and dates?

A. Yes, I can. I started discussing duo-C.V.P. in 1960 or '61 with a number of physicians in preparation for a project that I was going to conduct. The names are Milton Gottlieb, M.D., Ronald Okun, M.D., Travis Winsor, M.D., Isadore Ferrie, M.D., Sidney Wiseman, M.D. There were a number of them.

Q. Have you ever heard of any adverse reports with [236] respect to the safety of C.V.P. or duo-C.V.P. when used in treating abnormal capillary permeability or fragility?

A. Absolutely never.

Q. Have you ever read of any such adverse reports?

A. Never.

The COURT. So to save you time, I haven't heard any testimony of any adverse effects other than reaching an adverse effect by saying by being lulled into using it the patient doesn't get the benefit of something he ought to have.

Let's get in on that deal.

Mr. HOFFMAN. Fine.

By Mr. HOFFMAN:

Q. Do you have an opinion, doctor, whether on October 9, 1962, qualified experts generally recognized C.V.P. and duo-C.V.P. as safe for use in bleeding states associated with capillary, abnormal capillary fragility and permeability?

A. Yes, I do.



Q. What is that opinion?

A. At that time and at the present time I have never heard any qualified expert until today say that duo-C.V.P. or C.V.P. was in any way potentially harmful.

Q. Then if I understand you correctly, moving to my next question, in fact, your opinion today is that today qualified experts generally recognize C.V.P. and duo-C.V.P. as safe for use in the conditions recommended in the label?

[237] A. Absolutely.

Q. Have you reviewed the labeling of the products C.V.P. and duo-C.V.P.?

A. Yes, I have reviewed it, yes.

Q. Doctor, what is your understanding of the conditions for which C.V.P. and duo-C.V.P. are offered?

A. Abnormal capillary fragility or ulcerated capillary permeability.

Q. Doctor, I would like to show you the famous exhibits A through K, and specifically direct your attention to page four of Exhibit C. Is it your opinion, doctor, that a physician would understand that labeling to recommend the product for use in the underlying conditions?

Mr. EPSTEIN. Objection, your Honor. I think he can testify as to his understanding of it as Dr. Spaet did this morning, but not as to what the general state of some physician's mind might be.

The COURT. Objection is overruled. I allowed Dr. Spaet. He said the average doctor to him would read it thus and thus. I will let this doctor say the same thing.

The WITNESS. As I read this and the following pages of this brochure, it is very clear to me that the brochure was attempting to point out the results of research studies that had been collected and had been published in a brochure and that these are simply quoting what the research [238] studies and summarizing what the research studies had indicated. Whether anyone agrees with the research studies or not, these are simply quotations from those studies. When they have the little thirty-one and forty-six things, it means they are referring to specific paper, a specific research study.

The COURT. That is a footnote that supports it.



The WITNESS. In the back of the document they usually have fifty research studies, one, two, three, four, five.

The COURT. I understand.

The WITNESS. And each number is assigned to a specific individual, and this is a summary of those studies.

By Mr. HOFFMAN:

Q. Doctor, just to clean up the record, has your familiarity with the scientific literature continued since October 9, 1962?

A. Yes.

Q. Has your familiarity with the opinions of qualified experts continued since 1962?

A. Yes.

Q. So that the testimony you have recently given with respect to your opinion as to the opinions of qualified experts in 1962—I'm sorry—is the same for 1962 and [239] today?

A. I said yes. I thought they were exactly the same.

Q. Thank you.

Doctor, in your opinion, is it your opinion that the views of qualified experts, either in October 9, 1962 or today, would be that a lack of effectiveness for C.V.P. or duo-C.V.P. in treating abnormal capillary permeability and fragility would be regarded as presenting a safety question? Let me reframe that. I think I garbled it.

Is it your opinion that the opinions of qualified experts in 1962 and today are that a lack of effectiveness for C.V.P. in treating abnormal capillary permeability and fragility would be regarded as presenting a safety question?

A. I think it in no way presents a safety problem.

Q. Is it your opinion that the opinions of qualified experts would be the same?

A. Yes.

Mr. HOFFMAN. I have no further questions.

The COURT. Doctor, so that I will thoroughly understand you, I understand that you studied this subject matter and particularly these particular drugs in question here and that you have used them in your practice and know other doctors who have used them over a long period of time; [240] is that correct?

The WITNESS. Yes, sir.

The COURT. Based on your medical experience in the cases that you have used on your own and in experiences of other

doctors that you personally know about, have they had a positive effect for affecting this capillary situation that is referred to?

The WITNESS. I think they have had a positive effect in certain measured cases. The problem is, as was not really gone into this morning, frequently we look at the end result of the problem. I think one of the important things to distinguish in any agent is the difference between treating a symptom and treating a disease. Capillary fragility is a symptom of disease. You want to treat both things. If they had a symptom of brain tumor you want to treat the pain as well as the brain tumor.

The COURT. You can have headaches without having a brain tumor.

The WITNESS. Yes, sir.

The COURT. Don't give me that symptom.

The WITNESS. What I mean is because you may have a brain tumor doesn't mean you shouldn't treat the headache. And by the same token if you have capillary fragility and duo-C.V.P. is effective in improving capillary fragility it doesn't—

[241] The COURT. Do you mean it has a positive effect in your experience based on your experience with the product?

The WITNESS. Yes, it has.

The COURT. And in the treatment of the symptom?

The WITNESS. Yes, it has, in selected cases, absolutely.

The COURT. In no case as far as your knowledge is concerned has it had an adverse effect, a harmful effect?

The WITNESS. Not only in my personal knowledge but I have never heard of a harmful effect.

The COURT. You heard of some this morning.

The WITNESS. I did not. What I heard was that someone wasn't treating—

The COURT. You heard it was harmful if you use this and, therefore, did not use what you ought to have used and you died as a result of not using what you ought to have used; therefore this becomes harmful.

The WITNESS. But, sir, that line of reasoning is like saying you shouldn't give kapectate for diarrhea, if a serious illness is causing it. You still treat the symptom as well as the illness.

The COURT. You do it anyway.

The WITNESS. You treat both the things. When you treat the symptom you still look for the cause of the illness and you shouldn't negate looking for the cause.

[242] The COURT. All right. I understand your position. I just wanted to get it.

All right. Thank you.

Mr. HOFFMAN. Your Honor, could I follow up on that with one question?

The COURT. Yes.

By Mr. HOFFMAN:

Q. Doctor, directing your attention again to the labeling and, rather, the exhibits that are before you, without attempting to characterize them as labeling, you have reviewed those prior to your appearance here this morning, is that correct? Is that true?

A. Yes.

Q. Is there anything in those exhibits, doctor, which says to you either expressly or by implication that C.V.P. or duo-C.V.P. or for that matter any of the products covered by those documents are to be the exclusive therapy in any given situation?

A. Nothing that I can recall.

Q. Nothing that you can recall. Would you like to take as much time as you care to go through with it?

The COURT. I will not give him that much time to read it all.

You know it doesn't purport to say exclusive. They don't claim it does. You people keep putting up straws [243]—straw-men and then knocking them down.

Mr. HOFFMAN. We heard it from Dr. Spaet, your Honor. I just wanted to cover it. We will be satisfied with that.

I have no further questions.

The COURT. All right.

Whichever one of you want to examine this doctor.

#### CROSS EXAMINATION

By Mr. EPSTEIN:

Q. Doctor, you indicated that you used C.V.P. in your practice?

A. Yes, I have, sir.

Q. Would you tell me, doctor, what percentage of your current practice is devoted to seeing patients on a day-to-day basis? How many a patients a day do you see, doctor?

A. There are some days when I'm not in the office, but as a rule anywhere between ten and forty a day.

Q. Doctor, you indicated that your interest and your curriculum vitae indicates that your special interest is in cardiovascular diseases?

A. Yes, sir.

Q. Are you a specialist in hematology?

A. No, I am not a specialist in hematology. I am a specialist in cardiovascular diseases.

[244] Q. Are you board certified in hematology?

A. No, I am not.

Q. You talked about the fact that you didn't think that these drugs were potentially harmful. In the course of your practice on a day-to-day basis, the patients that you see, do you see patients who have a condition of habitual and threatened abortion?

A. No, I don't.

Q. Do you in that case, can you tell me on what basis you would recommend the use of C.V.P. in that kind of a situation, doctor?

A. I would recommend it in the way that I know that some medicologists have used it.

Q. No, I'm asking for your opinion.

The COURT. No. Let him answer it. He recommended it the same as he knows his own knowledge that some gynecologists have used it and the gynecologists feel in this subject matter.

Let him answer it.

The WITNESS. I practice in a very sophisticated area. I have doctors who are specialists in the hospitals that we use, and I know that many physicians who are looking for habitual abortions will look through all the medical causes they can and frequently not finding them will treat for a cause or treat any way they can to make the abortions discontinue. [245] I don't see patients with this problem because when I see them I refer them to a competent gynecologist who has more competency in the matter than I have.

By Mr. EPSTEIN:

Q. Do you treat patients on a day-to-day basis that you see for postpartum bleeding?

A. No.

Q. Do you treat patients for epistaxis?

A. Occasionally.

Q. About how many, doctor?

A. How many in what period, sir?

Q. In a month.

A. In a month, maybe two or three.

Q. Do you treat patients who have had tonsilectomies?

A. No.

Q. Do you treat patients who have hypertension?

A. Yes.

Q. Do you treat patients who have little strokes?

A. Yes.

The COURT. Get me that—just to—I am getting a lot of medical education—but what has hypertension got to do with bleeding?

The WITNESS. Are you asking me, sir?

The COURT. Yes.

[246]

The WITNESS. It has to do—There are a number of areas where hypertension is very important to bleeding. For example, people who have hypertension can develop bleeding intra-cerebrally and can develop strokes on that basis.

The COURT. Bleeding follows from it but hypertension is not bleeding, is it?

The WITNESS. No, absolutely not, but I think one of the points—

The COURT. You mean that is one of the residuals?

The WITNESS. That's one of the residuals of hypertension. Hypertension itself—

The COURT. Hypertension itself has nothing to do with bleeding.

The WITNESS. No. Hypertension itself is harmless. The problem with hypertension is the complications of it.

The COURT. You mean what follows from it?

The WITNESS. What follows from it.

The COURT. And what causes it.

The WITNESS. What causes it.

Mr. HOFFMAN. Your Honor, if I may be heard, I think what Mr. Epstein is now attempting is to attack the qualifications of this witness.

[247] The COURT. I think he has a right to do that.

Mr. HOFFMAN. I thought he stipulated to the qualifications when we first got it out.

The COURT. He stipulated he was an expert, and I have ruled that he is but all experts are not equally qualified. Obviously it

is a proper way to find out what he knows. This doctor seems to be doing very well handling himself.

By Mr. EPSTEIN:

Q. Doctor, do you treat patients with diabetic retinitis?

A. With a diabetic retinopathy, I do.

Q. How about a diabetic retinitis?

A. Is there a difference?

Q. I would ask you: Is there a difference?

A. Retinopathy means the general illness, a diabetic inflammation of the back of the ear. Retinitis means acute inflammation. If I had someone who had acute inflammation—

The COURT. Acute means present.

The WITNESS. Real sudden onset, your Honor, diabetic retinitis, but retinopathy is a general term.

You can use diabetic retinitis on chronic cases where it has been present for a long period of time. Yes, those patients I do treat.

[248] By Mr. EPSTEIN:

Q. Do you treat those patients regularly with C.V.P. products?

A. Not regularly, no.

The COURT. Do you use those products with these type of patients?

The WITNESS. Have I used it? Yes, I have, sir.

The COURT. With harmful or positive effects?

The WITNESS. Never with a harmful effect. I have never seen a harmful effect with duo-C.V.P. in my life.

The COURT. I am talking about the patients you used on this particular ailment that he is talking about.

The WITNESS. None, no, sir.

The COURT. Did it have any positive effect?

The WITNESS. Yes, on occasion.

The COURT. All right.

By Mr. EPSTEIN:

Q. Did the diabetic—Did the retinitis go into remission or become cured as the result of the use of C.V.P., doctor?

A. I would say that it did not progress on the cases I used it on.

The COURT. Aren't we getting way afield? I thought if you had diabetes that you never got cured. I [249] thought rest was the very best. Am I very wrong about that?



Mr. EPSTEIN. No. We're talking about diabetic retinitis, sir. I'm sorry.

Mr. HOFFMAN. Your Honor, I thought we were talking about capillary fragility and permeability.

The COURT. We have covered everything in the medical horizon.

By Mr. EPSTEIN:

Q. Do you treat patients with menorrhagia?

A. Not complex. If it is simple, I do. Usually if there is any problem that persists I refer to a gynecologist.

Q. Do you regularly treat such patient with C.V.P. products?

A. On occasion.

Q. Do you regularly treat them with C.V.P. products?

A. No. On occasion, I said.

Q. Do you treat patients with rheumatoid arthritis?

A. Yes.

Q. Do you regularly treat patients on a regular basis with rheumatoid arthritis?

A. Yes.

Q. Do you treat patients who have hemorrhagic [250] duodenal ulcers?

A. Yes.

Q. Do you see them regularly?

A. Yes.

Q. Do you treat such patients regularly with C.V.P. products?

A. No. I treat none of them with C.V.P. products.

Q. How about hemorrhagic cystitis? Do you treat patients that have hemorrhagic cystitis?

A. No. I see them on occasion but I don't treat it.

Q. What do you do with those patients?

A. I refer them to a proper urologist.

Q. Do you give them C.V.P. products when they are in your office before you refer them to a urologist?

A. No.

Q. Do you use C.V.P. products at all on such a patient?

A. I have not used them on that particular brand of patient.

Q. As to post-operative bleeding, I assume that you have surgery from time to time—do you deal with patients who have post-operative bleeding?

A. Do I see patients with post-operative bleeding?

Q. Yes.

[251] A. Yes, I do.

Q. Do you see patients that have post-operatives bleeding as a regular course with a C.V.P. product?

A. No.

Q. As to radiation therapy, do you see any patients that require radiation therapy.

The COURT. Do you contend—You're getting awfully far—I don't object—this doctor, as I say, seems to be very broadly based as far as his experience is concerned. But post-operative bleeding is major bleeding basically from a surgical standpoint. Do you contend that these pills are—

Mr. EPSTEIN. Well, your Honor—

The COURT. Wait a minute. Do you contend that a surgeon with post-operative bleeding would put somebody on some bio-flavonoid with Vitamin C or X or K?

Mr. EPSTEIN. I'm not a doctor, and I'm reading it, and it says here in Exhibit C in bold letters "post-operative bleeding," and it says underneath in bold letters in one sentence "But administered pre-post-operatively, C.V.P. had a salutary effect on capillary bleeding and hastened healing following surgical procedures."

All I can say to you is that I will submit on my own course I don't want any doctor to give me C.V.P. if I have post-operative bleeding.

[253]

# REDIRECT EXAMINATION

By Mr. HOFFMAN:

[255]

Q. Doctor, you aren't a hematologist, are you?

A. No, I'm not.

Q. What is your specialty?

A. I am a specialist in cardiovascular diseases.

Q. Do you consider that hematology is the only specialty whose members are experts qualified to evaluate the safety or effectiveness of drugs such as C.V.P. or duo-C.V.P.?

A. Absolutely not.

Q. Do you believe that your specialty is such a specialty?

A. Of course I do. You're dealing with—

The COURT. You wouldn't expect him to say no in either event.

The WITNESS. I can substantiate it easy by saying you are dealing with the pipe and the water in the pipe and it's the same



thing with the blood and the pipes that [256] carry the blood. You know they both involve the same thing.

The COURT. You handle the pipes.

The WITNESS. I handle the pipes and the heart, the pump, and the hematologist takes care of the stuff that goes inside.

The COURT. So you must know what goes through your pipes—

The WITNESS. Exactly.

The COURT (continuing). And he ought to know whether the pipe is rusty or not.

The WITNESS. Exactly. I will respect his opinion to a certain extent.

The COURT. All right.

Thank you.

Mr. HOFFMAN. No further questions.

The COURT. Step down.

(Witness excused.)

The COURT. Call your next witness.

Mr. HOFFMAN. Dr. Clemetson, please.

Whereupon,

[C. Alan B. Clemetson was called as a witness and, having been first duly sworn, was examined and testified as follows:]

(Dr. Clemetson's curriculum vitae was marked for identification as Plaintiff's Exhibit No. 6.)

[257] Mr. EPSTEIN. Your Honor, the defendant will stipulate the contents of the curriculum vitae of C. Alan B. Clemetson, M.D., that has been delivered to us, including attached thereto the bibliography of Dr. Clemetson to the items of twenty-three published papers.

The COURT. All right. Let them be admitted and I will accept the doctor as a very qualified expert in the medical field and let him testify accordingly.

The CLERK. Plaintiff No. 6.

Plaintiff's Exhibit No. 6, heretofore marked for identification, was received in evidence.)

#### DIRECT EXAMINATION

By Mr. HOFFMAN:

Q. Doctor, will you state your name for the record, please?

A. C. Alan B. Clemetson.

Q. Doctor, your curriculum vitae has been introduced into evidence. Can you tell us what your present professional position is?

A. I am director of the Department of Obstetrics and Gynecology at the Methodist Hospital in Brooklyn, and I am an associate professor at the Downstate Medical Center of the State University of New York.

Q. Do you consider these major hospitals and teaching institutions?

[258] A. Most certainly.

Q. Are you personally acquainted with C.V.P. and duo-C.V.P.?

A. I am. Not—I have only used the duo-C.V.P.

Q. Can you tell us the circumstances in which you became familiar with them?

A. In 1959 or '60, I was teaching at the University of Saskatchewan in Canada, and I conducted a study of the treatment of women who had excessive menstrual bleeding associated with capillary fragility, easy bruising and sometimes bleeding gums, and in this study we used both the genuine duo-C.V.P. and lactose placebo capsules which were double-blind labelled, one was labeled X and the other Y, and we didn't know at the beginning of the study which was which. All the patients had one month without any treatment, and I had a lady technician who would go every day to the patient's home to test the capillary strength, the skin of the arm with a suction machine. She would find out how many pads had got soaked and in some cases we used a measure of blood loss.

In this study there was no doubt whatsoever that eight out of ten of the women who had this kind of bleeding problem were improved by the product.

Q. Was this study ever published, doctor?

A. It was published in the American Journal of [259] Obstetrics and Gynecology in 1962.

Q. Do you use C.V.P. in your practice?

A. I do.

Q. For how long have you?

A. Since I first discovered its effectiveness in 1959 or '60.

Q. In the course of your studies and use of the duo-C.V.P. have you had occasion to become familiar with the scientific literature dealing with bioflavonoids?

A. Yes.

Q. And specifically with duo-C.V.P.?

A. Yes, I have.

Q. Have you discussed duo-C.V.P. with other experts?

A. Yes.

Q. Can you give us some names and dates, please?

A. Oh, I have spoken to so many people in France, in—

The COURT. It is not going to do any good to fill the record with names. I mean I will accept it if he says he discussed it with other doctors, certainly I will agree that he has.

I wouldn't expect him to tell me he had if he didn't.

He says he has. That is sufficient for me.

[260] By Mr. HOFFMAN:

Q. Doctor Clemetson, have you ever read or heard of any adverse reports on the safety of duo-C.V.P.?

A. Not until today. Well, that was not a report, but we had these statements that they might be dangerous which until this time I have never heard of anything to that effect, and I would say that they would probably be one of the safest of all drugs on the market today. They are mild. They are slow in effect. They take a month or two to have effect but the effect is beneficial always. I have never seen a harmful effect from this product and that is more than you can say for most of the drugs that the hematologists use which are very potent drugs which can kill if you double the dose.

Q. Doctor, let me direct your attention to the packet of materials, Exhibit Nos. A to K that I believe you have before you. Have you?

A. No, I have not read them.

Q. Have you seen these?

A. No, I haven't. I am familiar with the labeling.

Q. You are familiar with the labeling?

A. I have seen it in the past but I haven't read this stuff.

Q. Doctor Clemetson, would you say that your previous [261] comments as to not having read or heard of adverse reports on the safety of duo-C.V.P. would apply to the use of C.V.P. in the conditions in the labeling with which you are familiar as well as just generally?

A. Most of the implications of the labeling, that it is good for conditions associated—for the capillary fragility associated with various conditions I would agree with.

I must say I could not agree, I haven't read the labeling, I couldn't agree with the treatment of postpartum hemorrhage, which is in here. It seems to come up. I haven't seen it, but that I do not agree with. I mean I wouldn't treat a patient with postpartum hemorrhage with this. But I mean a patient with capillary fragility is a different thing altogether. I mean maybe they left a bit of placenta in and that is why she's got post-

partum hemorrhage. Nobody in their right sense is going to treat that.

Q. Doctor, directing your attention to the celebrated page four of Exhibit C, I wonder if you would read to yourself the material in bold face beginning with the words——

The COURT. What he is asking you, doctor, is to have you read the whole thing, the headlines at the top and then this part which does refer to this postpartum.

The WITNESS. I mean I take objection to the postpartum. I am not going to be associated with that.

[262] I think for the use of threatened abortion or recurrent abortion, I have read Javits' work on this, I have read Greenblatt's work on this, and although I haven't conducted a controlled study myself I have found it useful for this purpose.

By Mr. HOFFMAN:

Q. For controlling abnormal capillary fragility and permeability?

A. Associated with this threatened abortion.

Q. Doctor, do you have an opinion whether on October 9, 1962, qualified experts generally recognized that C.V.P. products were safe for use in the conditions you have just mentioned?

A. Their safety was never questioned. Their efficacy, yes. Efficacy has been questioned, but safety, never.

Q. Doctor, do you consider that the use of duo-C.V.P. in treating the conditions you have mentioned would be unsafe by reason of an alleged lack of effectiveness?

A. No. I think this is a specious argument.

Q. Do these opinions that you have expressed as to the state of expert opinion in 1962 apply, in your opinion, apply to the state of expert opinion today?

A. What I just said?

Q. Yes.

[263] A. I think this is true today, just as it was then.

The COURT. All right.

Do you have any questions?

#### CROSS EXAMINATION

By Mr. EPSTEIN.

Q. Doctor, you made a statement that hematologists used drugs that a double dosage could kill. What kind of drugs were you referring to that hematologists use?

A. I was thinking of dicoumeral. The Food and Drug Administration is particularly interested in drugs which have a demonstrable pharmacological affect, such as the drug like dicoumeral, which will half the clotting time of the blood, and if you double the dose you kill the patient. This is perfectly safe according to the F.D.A.

Q. Isn't this——

The COURT. Let him read it.

Mr. EPSTEIN. I'm sorry.

The COURT. Don't interfere with him.

The WITNESS. What I am saying is that the Food and Drug Administration would approve this kind of drug for use even though a double dose can easily kill a patient by their bleeding to death, but because it has a known pharmacological effect they assume it must be beneficial for the patient. In actual fact, twenty years have now gone by [264] with use of dicoumeral for the treatment of coronary thrombosis and now we begin to get questions as to whether in fact the patients are living any longer or not. It has a proven effect but is it beneficial? I say duo-C.V.P. is beneficial even though we cannot prove very easily how it works. It is utterly safe and beneficial and maybe the F.D.A. should concern itself with the dangerous drugs.

By Mr. EPSTEIN:

Q. Doctor, when you say that C.V.P. is safe, are you telling me that it is safe because there is no toxic reaction in the patients that you have observed?

A. You can give ten times the dose without any harm. I have never done it, but you could.

Q. I am asking you specifically are you telling me it is safe because you have never observed a toxic reaction in a patient to whom you have administered it?

A. From that point of view it is safe and I think from the other point of view it is equally safe because I rely on the intelligence of the doctor, as he pointed out before, if you have capillary fragility and brain tumor no doctor is going to imagine that by treating the capillary fragility the brain tumor will go away. You have to rely on the intelligence of the doctor to know what he is treating.

Q. Doctor, on that statement, when you say that C.V.P. is safe because it doesn't have a toxic reaction, [265] are you also telling me that it is safe to give—Would your answer be that it is safe to give a patient a drug which you know that there is a drug of better or first choice therapy in a given disease situation?

A. I am glad you brought that up because the question was raised this morning, how do you treat capillary fragility——

Q. No. I want to know what——

The COURT. Let him answer.

Mr. EPSTEIN. All right, sir.

The COURT. You have asked him. Now he is entitled to answer it.

The WITNESS. We had evidence from the hematologist this morning concerning the causes of capillary fragility. Now, when a patient comes in with a bleeding problem what happens is that all the tests that can be done in the lab are ordered and the blood is sent down——

Mr. EPSTEIN. Doctor——

The COURT. Let him finish.

Mr. EPSTEIN. I'm sorry.

The WITNESS. I'm sorry.

The COURT. I think it is fair to let him finish.

The WITNESS. The blood is sent down to the laboratory. The hematologist gets the blood. The blood [266] vessel stays up with the patient and the doctor who has to treat the patient.

Now, the hematologist is an expert in clotting and whether blood will clot or not, and C.V.P. has no function whatsoever in any of these clotting problems in which the hematologists are experts. It is good for the vessel wall. Now ninety-nine out of a hundred patients who have these excessive bleeding problems that I treat, the excessive menstruation, first we have to rule out cancer. Then we have to rule out pregnancy. We have abortion. We have to rule out other kinds of disease and we are left with a group of patients who have capillary fragility and excessive bleeding. I send their blood to the hematologist. Ninety-nine times out of a hundred there is not clotting disorder, but I am left with the patient with capillary fragility. He doesn't get her. He gets the clotting problem. I've got the patient with the excessive menstrual bleeding. And there is no——

The COURT. Doctor, what you are saying——

The WITNESS. What I am coming to at the end there is no alternative treatment except cortisone and cortisone is very, very potent and a very, very dangerous drug. I don't know of an alternative except you can put them on the contraceptive pill. That is one way, and the other way is to treat them with this, which is a very mild beneficial and harmless drug, and——

[267] The COURT. So what you are saying, doctor——



The WITNESS (continuing). So if you had an alternative which was better you could condemn this, but in the absence of an alternative the argument does not hold up.

The COURT. What you are saying, doctor, is that from a hematologist's standpoint it may not have any effect as far as clotting is concerned.

The WITNESS. It does not affect clotting at all.

The COURT. But because it does not have any effect on clotting does not say that it does not have any effect on the other symptoms or causes of this capillary disorder. That is what you are saying?

The WITNESS. Exactly so, sir.

The COURT. That sounds rather logical.

Mr. EPSTEIN. Now, may I ask him my question again, your Honor?

The COURT. Yes. He answered it, I thought.

Mr. EPSTEIN. No. I think what I asked him and what I would still like the answer to this—

The COURT. You want to know if there was a better substitute would it be harmful, and he said first there is no better substitute except cortisone.

Mr. EPSTEIN. I didn't ask him about C.V.P. products. That is where we launched into this discourse.

[268] I had asked him as a physician if there is a drug of better choice, if there is a preferred treatment do you give a lesser treatment, does he consider it safe. That is all I wanted to know. I think it would be a yes or no answer.

Mr. HOFFMAN. Your Honor, the answer—

Mr. EPSTEIN. We have listened to what he said. I just want him to answer my question.

The COURT. Gentlemen.

Mr. HOFFMAN. I objected to the question.

The COURT. Gentlemen. I know it is getting late but let's keep your seats.

I will say he does not have to answer the question. It is theoretical. It doesn't mean anything. It is one of these stop beating your wife questions.

Come on, let's get on with the case. I mean what has that got to do with it? Different people do not all use the same drug for anything, and it would be awfully hard for me to be convinced of that. There is not an absolute certainty in any med-

ical treatment. Most of them use the process of elimination in order to find out what is right to do under a particular circumstance. Isn't that right, doctor?

The WITNESS. Absolutely, sir.

The COURT. There is no absolute certainty and pick out of this bottle and that is a cure for everything.

[269] The WITNESS. No. I think the F.D.A. wishes medicine were a science.

The COURT. Let's get on with it.

By Mr. EPSTEIN:

Q. Doctor, do you treat patients with hemorrhagic duodenal ulcer?

A. No. I treat only women for gynecological and obstetrical conditions.

Q. So that as to the list of diseases or ill states that are described in the Exhibit C—

The COURT. He said he has not read Exhibit C so I will not let you ask him anything about it. He said he hasn't read it. So there's no use for him to go over it. He is not familiar with it so he is not qualified to testify and he said he was not. So you can make the most of it. He said he hasn't read it. Is that right, doctor?

The WITNESS. Yes, sir.

By Mr. EPSTEIN:

Q. So then do I understand then, doctor, the extent of your knowledge and use of C.V.P. products is only then in the case of women who have gynecological or obstetrical problems, you have never been exposed to it other than that?

A. I have read a great deal other than that.

[271]

By Mr. EPSTEIN:

Q. Have you done any other experiments, doctor, any other clinical studies other than the one you have just described to us?

A. Yes, I have done many studies, but it is difficult to control them in the way that that first one was because it is very difficult to treat a patient for long with a placebo. If you start to give a patient sugar instead of [272] genuine treatment they are jolly soon back on your neck complaining that they aren't



getting better and you have to do something to give them genuine treatment and if you are going to give half your patients for three months, as in that study, a placebo, you very soon run into trouble and your colleagues who referred the patients to you start to object, so I haven't been able to continue as a controlled study, but I have continued to treat patients with this treatment with mostly beneficial results, some so beneficial that if this drug were withdrawn from the market I don't know what I would treat them with.

\* \* \* \* \*

[275] Whereupon,

[Murray Joseph Miller was called as a witness and, having been first duly sworn, was examined and testified as follows.]

(Dr. Miller's curriculum vitae was marked for identification as Plaintiff's Exhibit No. 7.)

The COURT. Let his qualifications be admitted and I will approve him on his qualifications as being an expert and permit him to testify to save time.

The CLERK. Plaintiff No. 7.

Mr. HOFFMAN. Thank you, your Honor.

(Plaintiff's Exhibit No. 7, heretofore marked for identification, was received in evidence.)

#### DIRECT EXAMINATION

By Mr. HOFFMAN:

Q. Would you state your name, please, for the record, doctor?

A. Murray J. Miller.

Q. And what is your present position?

A. I am chief of medicine and chief of staff at Quakertown Community Hospital and instructor in medicine at Hahnemann Medical College and Hospital.

Q. Are you acquainted with C.V.P. and duo-C.V.P.?

A. I am.

Q. Could you tell us the circumstances in which you [276] became acquainted with them?

A. I was assigned to the Naval Hospital in Annapolis, 1957 to 1959, as assistant chief of medicine. As one of my volunteer duties I was functioning as a coach and medical physician for the 150-pound football team, as a medical consultant to the wrestling team. We were troubled with quite a few soft tissue injuries from the contact sports and accordingly searched the literature to see if there was some medication that might be

of value in decreasing either the frequency or the severity of the soft tissue injuries.

Q. Have you used C.V.P. in your practice?

A. I have.

Q. Do you now?

A. I do.

Q. Has any of the research or studies that you were describing a moment ago with the C.V.P. products ever been published?

A. Yes, it has.

Q. Where?

A. I believe it was in 1960 in the Medical Times on the experimental work I did while at the Naval Academy.

Q. Doctor, in the course of your work with C.V.P. and your studies of the product, have you had occasion to become familiar with the scientific literature as to those products?

[277] A. A good bit of it.

Q. Have you discussed the C.V.P. products with other experts?

A. Yes.

Q. Have you ever heard or read of any adverse reports on the safety of C.V.P.?

A. None whatsoever.

Q. With respect to any condition of use?

A. None whatsoever to my knowledge.

Q. Do you have an opinion whether or not on October 9, 1962, qualified experts generally recognized that C.V.P. and duo-C.V.P. were safe for use in treating abnormal capillary permeability and fragility?

A. It was considered safe.

Q. Generally considered safe by qualified experts?

A. Yes, sir.

Q. Do you have the same opinion as to the state of expert opinion today?

A. Yes, I do.

Q. Did you hear the testimony of Dr. Spaet this morning?

A. Yes, I did.

Q. And of Dr. Corn this afternoon?

A. Yes I did.

Q. Do you recall what specialty they indicated they [278] practiced in?

A. They are hematologists.

Q. Do you recall hearing the list of underlying disease states that counsel for the defendants, Mr. Epstein, read part of to Drs. Karpman and Clemetson this afternoon?

A. Yes, I did.

Q. Is it your opinion that a hematologist would, if he had a medical practice, treat patients with those conditions?

A. To the best of my knowledge, hematologists' patients are usually referred to them by other physicians for problems of bleeding or blood components rather than the organs that they contain.

Q. I am not clear on the answer to the question.

The COURT. He made it clear to me.

Mr. HOFFMAN. Okay.

The COURT. He said their problems in the main were limited to questions of blood and blood quality and treatment.

The WITNESS. Yes, sir.

The COURT. They are specialists in blood itself and the actual product; isn't that right?

The WITNESS. Yes, sir, and the blood-forming organs.

[309] \* \* \*

Mr. HOFFMAN. Your Honor, respectfully, we do not think you determine the safety of the drug at all. We think what you have to determine is whether there was in 1962 a consensus of expert opinion that the product was safe, and we think the testimony of these witnesses, all five of them, shows that the consensus was, in fact, that the product was safe. The Defendants' witnesses said, "Ah, but there wasn't a consensus that the product was effective," and they went further than that, but that is as far as the Government had to go in this case, and because these two doctors said there was not a consensus that the product was effective there could not be a consensus that it was safe.

We do not think the Court has to determine, your Honor, whether the product was, in fact, safe. We do not even think the Court has to determine whether—I am sorry—we do not think the Court has to determine whether the product was, in fact, safe or, in fact, effective, and we do not even think the Court has to determine whether there was a consensus that the product was effective because we have made clear our position all along in this case that while we think the product is

effective we recognize that there was no consensus in favor of that effectiveness.

What there was a consensus in favor of, your Honor, was that the products were safe. \* \* \*

[314] \* \* \*

Well, your Honor, as with the zerex analogy we believe that this is false reasoning. We think it is an attempt to put something in the statute which is not there and for one thing, your Honor, as a question of statutory interpretation, it overlooks the fact that in 1962, when Congress wanted to add the concept of effectiveness, efficacy of the drug to the statute, it took an enormous legislative battle to do it, the Kefauver-Harris Amendment of 1962, following the thalidomide events.

So, for the Government now to say that the word "safety" which has been in the statute since 1938, all along meant that incorporated concepts of effectiveness, we think just misses the whole point.

Now, Dr. Spaet testified in his view that the product was not safe because it did not work, but he said it did not cause any harm by itself, that he never heard of any harm by itself, and the only basis on which he could say, the only basis on which he could give the conclusory testimony that in his view experts didn't think the product was safe was by relating it to this concept of efficacy.

[315] Dr. Corn, if your Honor will recall, if he ever got to give this testimony, and I am not entirely certain whether Mr. Epstein ever actually got him to say, was apparently prepared to say something like this.

The COURT. He said the same thing. I mean I cut him off somewhat and said clearly, Dr. Corn would have said, had he been allowed to ask, and I accepted it as such, that he would reach the safety factor by identically the same method that Dr. Spaet arrived at. In fact, I clarified that myself and said his opinion would be the same. So the mere fact that the Court, to save time, did not allow Mr. Epstein to go over each of the same questions, I will accept his testimony as duplicating, corroborating exactly what Spaet said.

Mr. HOFFMAN. Respectfully, your Honor, for the record, we would not so stipulate, but I understood the Court's ruling and I will move on.

Now, the question then is: What was the consensus? We think as a legal matter the concensus of expert opinion in 1962 was that the product was safe because of the legal deficiencies in this efficacy equal safety theory propounded by those two doctors, but beyond that, your Honor, the Government is probably going to tell you in their argument that whenever you have a conflict of opinion as to what the concensus is, that is one expert has gone around and taken a [316] concensus and he says one thing and another expert has gone around and taken another thing, the Government will tell you that that conflict means that there is no concensus, and they are going to cite to the Court, your Honor, two district court decisions of some vintage that seems to say something like that.

Respectfully, your Honor, we think that is simply not the law. \* \* \*

[320] Mr. HOFFMAN. That, your Honor, we would submit is Mr. Epstein's problem, but more importantly Dr. Spaet and Dr. Corn each did, in fact, go down both paths. We think they both said that, well, the product was generally recognized as non-toxic, so that to the extent that that is the governing premise and the one on which Drs. Karpman, Clemetson and Miller testified, Dr. Spaet also went down that path, and he did not disagree.

Your Honor, moving, if I may, briefly, from this point, because we think that this evidence does show that, No. 1, the expert concensus in 1962 was that the product was safe. We think all the doctors except possibly Dr. Corn, who may not have gotten to that, did say that, and he did not say anything to the contrary.

We think that under the relevant statutory meaning of the word safe the product was, therefore, generally recognized as safe, and we also think, of course, that the weight of the evidence is that even among doctors the word safe does not have that highly forced and far-fetched meaning that Dr. Spaet and Dr. Corn tried to give it.

We think that we have to go on and show that the other two prerequisites, so to speak, to the application of the grandfather clause were met, and we do not think there is any real dispute about one of them. The first, or I should [321] say the second prerequisite of the grandfather clause is whether a product was in commercial use and sale on October 9, 1962.

The COURT. Well, they do not dispute that.

Mr. HOFFMAN. There is no dispute about that.

The COURT. They do not dispute that. It was clearly in use at that time.

Mr. HOFFMAN. We will move past that, your Honor.

The other point has to do with whether the product was covered by an effective new drug application at that time because the statute, the grandfather clause says you are exempt from this new area of regulatory authority given to the commissioner in 1962 if, first, you were in commercial use in '62, which we are; second, if you were not a new drug on October 9, 1962, under the statute as it then stood, and this is the subject that your Honor and I have just been discussing; and, third, if on October 9, 1962, the product was not covered by an effective new drug application.

Now, this later point is a matter of no factual dispute and enormous legal dispute, and, of course, nothing whatever was said about this on Friday because it is not an evidentiary matter. The facts there is no disagreement on. The facts are that in 1955-56 some but not all of these products were the subject of new drug applications, which were [322] filed with the Food and Drug Administration and allowed to become effective. The fact, further, your Honor, we think as based on the evidence that we have just been discussing is that sometime thereafter the products ceased to be new drugs; they became through use, through use over a material time and to a material extent—

The COURT. You mean subsequent to '55.

Mr. HOFFMAN. Subsequent to '55, your Honor, they became through this material time, material use generally recognized as safe and no longer new drugs, again the point we have just been discussing.

And so, your Honor, the Food and Drug Administration actually recognized in a series of letters which were put into the record by stipulation and the relevance of that I think, without meaning to belabor the point, because it did come up very briefly on Friday, is that the Food and Drug Administration is the official agency which is responsible for administering the Food and Drug Act, and while they do not conduct proceedings to determine it, they do have some expertise in deciding whether a product is a new drug or not a new drug.

That is what Dr. Smith's business was. He is the man who wrote those letters, or most of them, and he said the products were no longer new drugs.

\*     \*     \*     \*     \*



[326] \* \* \*

Mr. HOFFMAN. Because all I am saying is that this bioflavonoid, this citrus flavonoid compound which is in the C.V.P. products having been on the market before and being an old drug can continue to be marketed and to the extent that it is put up in a new package or something like that if the claims are the same and the ingredient is the same this product is not a new drug. It does not make it a new product just because you might put a new package on it, if the claims are the same. It does not make it a new drug—well, it might be a new drug if you added something to it, but then the bioflavonoid part of it would not be a new drug.

The COURT. If you mix it with something else doesn't it become new?

Mr. HOFFMAN. To the extent that something new was added it would be new and that is all, and that is what Dr. Smith recognized in 1961, your Honor, in those letters when he said that to the extent that the citrus bioflavonoid compound is involved this is not a new drug. So he was recognizing, as he had previously, that through general use over a period of time the citrus flavonoid compound products [327] manufactured by Plaintiff were not new drugs.

Now, it is our position that as a matter of law, and we are just relying on these FDA letters by way of dramatizing the position, to the effect that they agreed with us then. We say that as a matter of law, the products then were no longer covered by an effective new drug application and the Government says, well, yes, they were because once covered always covered; you filed it and therefore you were covered.

Now, your Honor, respectfully, there is absolutely nothing to support that once covered always covered approach except what Government counsel says. There is nothing. There is no legislative history. There are no cases. There is nothing in the statute. They just say it as if it were a verity.

But I think we have to look a little beyond that and see what happens to a product when it is covered by an effective new drug application. Even then in 1962 certain things needed to be done. There was an on-going system of administrative controls.

Now, it is our position, your Honor, that once a product became no longer new and the agency's own regulations at the time recognized that such a thing could happen, the product

ceased to be covered by an effective new drug application. The company could when it concluded that the [328] product was no longer new have withdrawn its new drug application. It could, so to speak, have gone down and asked for its copy back or if that was not precise procedure effected a withdrawal so that the thing was no longer carried on the books; but that is a matter of form, your Honor, and we think——

The COURT. If they did not withdraw it what happens?

Mr. HOFFMAN. We think that the product still was no longer covered by an effective new drug application because unless the phrase is just a meaningless repetition of abstractions, it has to have some content. The only content can be, first, does the product need that effective new drug application to be marketed and, second, is it subject to the on-going administrative controls of FDA, and the answer is in this case, even though the piece of paper remained in the files, neither of those things were true, so that the product as a practical matter was no longer covered by an effective new drug application on October 9, 1962.

[331] \* \* \*

So we have this system of on-going administrative controls which we think represents the real meaning of the phrase covered by an effective NDA, and we think further that our products were not covered by an effective NDA on [332] October 9, 1962, because the products having ceased to be new were no longer subject to that system; they were just as if the products had never been NDAed. They were just as if the product from the moment of its conception had been generally recognized as safe.

The COURT. If I understand you correct, and I will accept this unless the Government corrects it, corrects you or questions you, do I understand that a new drug applications prior to 1962 automatically became inoperable by statute after the passing of time unless there was some ruling or contrary evidence promulgated by the Food and Drug Administration. In other words, if I filed a new drug application strictly in accordance with law in 1950, and I consistently marketed the drug up until 1962, strictly in accordance with statutory requirements, I am talking about this old drug that I got the application—now, by statute, I understand you to say it automatically become old because over this period of time—I mean assuming



it had been factually accepted in the market and constantly used, that it automatically became an old drug and, therefore, did not come under this present Act.

Mr. HOFFMAN. Well, automatically may have connotations that may be confused.

The COURT. It has to become old—what I am getting at and I want you to get your position, it either [333] becomes old by the passing of time and use—

Mr. HOFFMAN. That is right, your Honor.

The COURT (continuing). Or it becomes old by operation of statute.

Mr. HOFFMAN. The statute did not say anything about it. In effect, the new drug application became obsolete, because in the passage of time the drug became old, it no longer needed the application to be marketed and the application just became superfluous through the passage of time. That is the essence of our position.

The COURT. All right.

[350] \* \* \*

The COURT. I only read, too, Mr. Epstein, but, unfortunately, everybody does not read the same. I mean we look at the print, but we do not come up with the same impression. Now, read the whole thing. What does it say? I mean you have to read it all. You cannot read things out of context.

Mr. EPSTEIN. I read it—

The COURT. Look at any of those exhibits, and, clearly, what does it say? It has a great big triple headline on the front page, and you would clearly have to read that the tonsillectomy it referred to was not the cutting out of the tonsils—that is a tonsillectomy—it was not designed to stop bleeding, the obvious bleeding, that flows from the cutting out—a tonsillectomy. I do not know how you can read it to say that it did not refer to capillary fragility, and so forth, resulting therefrom. Now, is that not what it says?

Mr. EPSTEIN. No, it does not.

The COURT. Why doesn't it say it?

Mr. EPSTEIN. Well, because, in the labeling, Your Honor—

The COURT. I am talking about that page.

Mr. EPSTEIN. The same piece of labeling, and Dr. Spaet testified on that specific point, the representation was [351] made, "Clinically, the anti-hemorrhagic effect of C.V.P. products—"

The COURT. Dr. Spaet did not intrigue me too much on that testimony. All he said was, clearly, he could read that and it would not cause him to be taken in.

Mr. EPSTEIN. But the issue, Your Honor—

The COURT. Wait a minute. All he said was it would cause the average doctor in Northern Virginia to be taken in because the average doctor is not as smart as he is. I do not buy that argument, with all due respect to the doctor. He says he is a hematologist and "that would not take me in; it would not fool me at all, but the general practitioner that does all the work, that uses all these pills in Northern Virginia or in Northern New York"—he put both—"they would be taken in. They would buy this in the full expectation that it would stop an operational, post-operation, bleeding." I would say, if he got taken in that much, he ought to lose his license. It does not read that way to a layman. I just will not read it that way.

Mr. EPSTEIN. Well, Your Honor, the labeling for these products is directed to doctors. The layman never sees the labeling.

The COURT. I know, but it would not take me in as a layman. It certainly ought not to take a doctor in, should it?

[395] \* \* \*

[Mr. HOFFMAN]

It is true that for a year or two, or thereabouts, we submitted changes in the labeling to the Food and Drug Administration as required when a product is still a new drug. Thereafter, we did not and, in fact, the correspondence between FDA and our company which is in the record and about which there was some discussion, was correspondence that really was concerned with that question, whether we had to or [396] not, and the thrust of those letters being that the citrus flavonoid C.V.P. element was no longer a new drug, we stopped submitting new labeling, we stopped submitting changes in the method of manufacture because we were no longer a new drug and, in fact, the Government has made that absolutely crystal clear in its admissions which are on file in this case because if your Honor will remember from Friday they said they did not have all the labeling that they could say was being used on October 9, 1962, that was not in the files. Why wasn't it in the files? Because we did not submit it.

Now, Food and Drug Administration regulations in force in 1962 contemplated precisely this situation.

The COURT. Wait a minute, so I will get it. You say that the record and the admissions here show that you have effectively withdrawn your new drug application previously introduced.

Mr. HOFFMAN. In practical effect it is if we had.

The COURT. I say effectively withdrawn as shown by your correspondence with the agency clearly indicating that you are not going to send any more because it is not a new drug.

Mr. HOFFMAN. That was the substance of it.

The COURT. And you are going to take your chances on seizure and let them seize be damn because it is an [307] old drug and once they seize and there is no new application you will defend the seizure; is that what you are saying?

Mr. HOFFMAN. Well, it was not in that posture of defiance, your Honor.

The COURT. I know you are not complaining—you are not encouraging a seizure but that is the net effect of it.

Mr. HOFFMAN. Well, it would be except in effect we had the agreement of Food and Drug Administration. The record includes the letter that we wrote in 1961 referring to the previous letters commenting that it would appear that this means that the agency no longer regards the products as new drugs.

\* \* \* \*

[418] The COURT. I did not take any evidence this morning.

Mr. HOFFMAN. Your Honor, I understand that.

Your Honor, this was never an issue in the case until it just came up at the close of the morning recess. We relied on their admissions in the answer, on the statements in their statement of material facts.

The COURT. That you had withdrawn?

Mr. HOFFMAN. Sir?

The COURT. That this application had been withdrawn?

Mr. HOFFMAN. No, not the legal conclusion that it had been withdrawn, and certainly not that a formal withdrawal document, something that looks like a will and testament had been filed.

The COURT. Do you say that there has never been an issue in here whether or not this application has been withdrawn?

Mr. HOFFMAN. We say it has never been an issue in here that for some years—

The COURT. Has it been conceded it has been withdrawn?

Mr. HOFFMAN. Your Honor, we are not contending it was withdrawn formally. We have always contended—

The COURT. I understand that. All I want to [419] get and really I just want to know what the record shows. You say that you now are—come under 107(4)—

Mr. HOFFMAN. Right, Your Honor.

The COURT (continuing). The parent grandfather—because you didn't have a NDA application pending because it had been withdrawn and they admit it has been withdrawn.

Mr. HOFFMAN. As your Honor said effectively withdrawn, practically speaking.

The COURT. That is right.

This is all the evidence you have in support of that?

Mr. HOFFMAN. This is the evidence and we have the documents here which are referred to in this paragraph of the complaint.

The COURT. Just pass them up.

Mr. HOFFMAN. All right.

The COURT. That is all I want is your evidence. I don't want him to stipulate anything.

Mr. HOFFMAN. There are three letters, one of which is in the record already as Exhibit C to the stipulation, and these are the other two.

The COURT. All right.

Mr. HOFFMAN. The sequence was a letter of February 28, 1961—

The COURT. All right. I just got this letter?

[420] Mr. HOFFMAN. Right, your Honor, February 28, 1961. It is a 2-pager. Then the letter responding to that is the letter—

The COURT. I don't have that. This is just asking them. Where is the letter?

Mr. HOFFMAN. The letter they wrote back is Exhibit C to the stipulation, your Honor. That was put in on Friday, and that is the letter of April, something, 1961, where the Commissioner said as to two of the products we don't regard them as new drugs, and as to the others we don't have the current labeling before us, and, of course, they didn't have it because it hadn't been submitted because the company no longer regarded the product as a new drug.

So he said I will agree or disagree with your position—

The COURT. Look. I don't want you to argue. I just want you to hand me the information. I am going to look at it myself—

Mr. HOFFMAN. Okay, your Honor.

The COURT. I am looking at what you have.

Mr. HOFFMAN. This was——

The COURT. Give me C.

Mr. HOFFMAN. Exhibit C.

The COURT. Is this all you have?

Mr. HOFFMAN. No, your Honor. Then there is [421] the third letter.

The COURT. Exhibit C.

Mr. EPSTEIN. Do you want this back?

Mr. HOFFMAN. No. That is your copy. You may have it.

Mr. SMONSKEY. I know where it is in the file.

Mr. HOFFMAN. Perhaps Mr. Smonskey can help us on that.

Mr. SMONSKEY. Exhibit C is right in there.

The COURT. That is all I want.

Mr. HOFFMAN. Exhibit C, your Honor.

The COURT. All right.

Mr. HOFFMAN. And then the third letter responding to Exhibit C.

The COURT. All right. Just give it to me.

Mr. HOFFMAN. I believe that was handed up, your Honor. There were two letters that I just handed up.

The COURT. That is right, two attached to it. They are both requests for the status. That is all those letters are.

Mr. HOFFMAN. No, your Honor. May 16, 1961, says, "This is in reference to your letter responding," and it says, "It is our recollection that the C.V.P. class of products," and this is the third paragraph, "were no longer considered to be new drugs the short time after the NDA became [422] effective." That was the statement of position.

The COURT. I understand that is what you say, but that isn't what they say.

Mr. HOFFMAN. They didn't respond.

The COURT. I see.

Mr. HOFFMAN. They didn't take a position.

Finally, your Honor, we have copies of a letter that was submitted to the Food and Drug Administration in 1965, in which the company—this was with regard to a collateral discussion——

The COURT. All right.

Mr. HOFFMAN (continuing). As to whether or not certain newly imposed reporting requirements that the Commissioner said were applicable to new drugs were applicable to these

products, and a sort of a semi-response was made to that request to comply with the reporting requirements with the final paragraph, "This information is being submitted with prejudice to our position that you do not have the legal authority to acquire reports with respect to drugs which are no longer new drugs and the submission of the above information——"

The COURT. All right. You do not need to read it to me. I will read it.

Mr. HOFFMAN (continuing). Does not constitute an implied information."

[423]

(Correspondence between HEW and USV Pharmaceutical was marked for identification and received in evidence as Plaintiff's Exhibit No. 8.)

The COURT. Do you have any other evidence? This is all you have?

Mr. HOFFMAN. The last fact I point to your Honor is that as conceded and stipulated in this case, in fact asserted in the answer, two of the products were never covered by an NDA by anyone's definition because no NDA was never even submitted for them. Those are the——

The COURT. They still reserve the right to do it. They say it is open in perpetuity.

Mr. HOFFMAN. They may say that we were entitled to it, but we never did. So we think what this demonstrates, your Honor——

The COURT. I don't want you to argue it. We will get that later. I don't want you to demonstrate anything. I have heard it.

Mr. HOFFMAN. Okay, your Honor.

The COURT. All right.

[441] \* \* \*

Mr. HOFFMAN. I would be delighted to close the presentation of the case and the plaintiff's argument and hopefully submit the case. There are only three simple points that I would like to make in response to Mr. Epstein.

One is that regrettably he is again wrong on the law when he says an applicant cannot come in and pull out his new-drug application because Section 130.8 of Title 21 of the Code of Federal Regulations says, and this has been in effect in substantially the same form for years and years, long before 1962, "The applicant may at any time withdraw his pending applica-



tion from consideration as a new-drug application upon written notification to FDA."

The COURT. I understand that.

Mr. HOFFMAN. All right.

The COURT. As I said, I don't even need a Federal regulation. He obviously can.

Mr. HOFFMAN. Okay. The next——

The COURT. But that doesn't help you much because you didn't give them that written application.

Mr. HOFFMAN. We did not give them the notice [442] in the language of the regulations. What we did do is write to them and say we think these products are no longer new drugs. Do you agree? And they said, Gee, we don't know. You haven't been sending in the labeling.

The COURT. Let me get you right down to the nub of this case. Are you willing to stipulate now and for the record, thereby estopping yourself from taking a different or an untenable position—I am not trying to box you, now, so be careful, in a corner that you can't get out of—that it was always, even though they did it a little clumsy and didn't have good expertise in the legal field and write the letter, you know, and crossing all the Ts, and so forth, as this section expressly provided; but that is what you intended to do all the time from way back 1962—'51—I mean——

Mr. HOFFMAN. From '57, your Honor.

The COURT (continuing). From there, yes, '57, that is what you intended to do all the time; you didn't write the letter because you did write to the government and you understood and relied on it that they accepted what you had done as a letter, at least that you thought that, so it was always your intention to withdraw this new-drug application and take whatever chances the law exposed you to for marketing it unapproved, and if you stand on that position now I am liable to accept you at it and then there won't be any question about them seizing you if they want to.

[444] . . .

The COURT. And you intended to withdraw your application. Now, I don't want any equivocation.

Mr. HOFFMAN. Your Honor, the statute uses the phrase——

The COURT. I don't want you to here argue with me any further. If you are telling me now that you didn't have the inten-

tion to do what you want me to read all of this stuff to draw the conclusion that you had an intention, I am liable to agree with you. Now, if you did have the intention I am inclined to agree with you. I like to help you do what you wanted to do.

Mr. HOFFMAN. Your Honor, I have to say that obviously the company, the company's business people and scientific people weren't thinking in the statutory terms, and I know that I certainly and our firm certainly was not involved with the company at that time, so I cannot say what was in their heads. I can say, and I can stipulate to this, that they intended by this correspondence and by continually asserting the position that these products were no longer new drugs that they no longer required an NDA in effect to be marketed and that——

The COURT. And they acted accordingly.

Mr. HOFFMAN. And they acted accordingly.

The COURT. From that date on they have treated [445] these as drugs to be marketed without a NDA approval?

Mr. HOFFMAN. That is exactly right, your Honor.

The COURT. All right.

Mr. HOFFMAN. Now, the only thing left, as I see it, is the Quinaglute case, which is I believe cited through the briefs that were—at least in our briefs filed a year ago. As Mrs. Sisk put it in the tail-end of her quotation or summary of the Senate Committee report, the question, even on taking them at their face value, is whether the product was effective for a life-threatening condition, and as your Honor has I hope made clear, I believe it is clear to us, the label used for this product was, is and has been abnormal capillary fragility and permeability. There is no suggestion in the record that that is a life-threatening disease regardless of whether the more serious disease states which accompany it may be, but those were not what the products were recommended for.

So, we say, your Honor, that Quinaglute has no application here. That is not authority for the position that the government asserts. The action of Congress in importing the concept of efficacy into the statute after a furious legislative battle in 1962 should be dispositive as to what the statute before that——

The COURT. Why do I get to that? Again I don't have to get to that in this case. You either come under the grandfather clause or you don't.

[446] Mr. HOFFMAN. We agree with that, your Honor.



The COURT. All right.

Mr. HOFFMAN (continuing). And we think we have proven all the elements.

[448] \* \* \*

By The COURT:

I also find without any difficulty that the question here—I think this statute is devisable. I think it does apply as both the government has aptly said and Mr. Hoffman has indicated that if it is a new-drug applicant, if it is a matter that is before the Food and Drug Act by virtue of a previously filed new-drug application approval form and is a continuing matter before the bureau by virtue of the continuing duties of notification, relabeling, remanufacturing, and the other prerequisites, I think it is the kind of a new-drug application that gives the Administrator under Section (b)(3) clause, as I will call it—3(b)(3) I guess you have characterized it, to have this two years, you know, hiatus, it will stand approved as of that date, and during this two-year period they can't do anything about it, and I think it is directly for the purpose of giving the manufacturer the opportunity to gather such data as he might need to have if he is called upon to submit any additional information in reference to both the old requirement, which was safety, and the new requirement or the new-coupled requirement of safety and efficacy.

[449] I think the 107(4) as I will call it, that is the final paragraph, is clearly a catchall which says in any case—in other words, if it is an old drug, one not pending, it just doesn't come before it and it is up to the government to do what they want to if they think that old drug doesn't meet minimal governmental standards for safety or efficacy. I think they have to get at it by seizure—I mean which is the basic way the government gets at it.

So, therefore, I now find myself in that unique position as to which category you fall in.

There is evidence here, and the government has admitted certain parts of it on admitting the so-called paragraph 9. The plaintiff augments that by some letters and so forth from various government officials, Dr. Smith particularly, certainly pertaining to his dealings with the bureau in connection with this matter; that is, he is inquiring whether they are considered old or new.

I have to assume, and I don't think it is a violent assumption, that a company of this size and type would have general knowledge of pending legislation, you know, effecting their product, and I would have to assume that the drug company knew that they were broadening the safety requirement by the amendment by including the word efficacy, or at least the government hoped to, and that it would probably apply from then on, because this would be '61, just before and [450] that is when some of this was going on, '60 and '61, just before the adoption of the Act in question or the effective date, and, of course, this hearing was going on before.

The company appeared to take the position that they were in the old drug. They say, and there is nothing to contradict them, that this record appears to show from then on they didn't change their label. If they did they didn't let the government know anything about it, and they didn't tell them anything more about it; and, as a matter of fact, they didn't do anything about it.

Now, they were trying to keep on both sides of everybody which isn't an unusual phenomenon, because when the bureau went into this new situation under the NAS investigation, under the paragraph 3, assuming it was an old—I mean an approved drug on the form and asked for additional data to support the safety and efficacy of the drugs in question, they did comply by giving—furnishing information—I mean I think that is clear, they did it, but I don't know that that makes it inconsistent, and it would have made it inconsistent, been fatal to that company had they not frankly stated in writing they were submitting this without prejudice, see, to their then and long standing claim that they weren't covered by that new-drug application because it just—they were not a new drug; but, nevertheless, they were going to give you this information in the hopes that we would stave off any [451] seizure or approval or whatever you might had in mind. Well, you can't hate them for doing that.

Now, we get back to the other question. You say this safety question—I am not interested in determining that other than using the—I mean this doctor's testimony that we had under the old-drug formula, as I call it, really is of little value to me other than it is testimony as to whether this drug was in fact a new or old drug in 1962—I am talking about factually, and notwithstanding the pendency of a drug application.

I would be of the opinion that even if it were an old drug, technically speaking, due to age and safe propensities, if there was a pending application, you know, approval form as a new drug that they had to go along, it hadn't been for any purpose withdrawn, it would still come under Section 3, because I think the only ones that are excluded in this last one are those who either didn't have an application or if they had a new-drug application it had been effectively and for all practical purposes withdrawn.

The definition of "safe" says it must have some effect. I think the exact word is reliance on the health. 268—I don't remember, but let's look at it. I think that is what it says—the statutory definition which is not always—it says, "The term 'safe' as used has reference to the health of a man."

[452] Well, if it is innocuous, if it is so nebulous that it is not good for anything as the government contended, and that is all the evidence they had, see—I mean all the government said it just was a harmless piece of some kind of juices extracted or chemicals extracted from citrus fruit coverings that might as well give them tap water; it just didn't mean anything.

Of course, other doctors disagreed with that, and even if they were correct that wouldn't take it out of the word of safe—I mean make it unsafe.

Thirdly and lastly, including the counsel's open admission and strong affirmance, I will assure you he can't back out of it if he comes to this Court; he will have an awful time backing out of it or anybody else, that it was always their intention if they did not fully and completely comply with the administrative requirement of writing an actual, technical, formal letter, saying, "I withdraw Application No. 32, per se," and sign it. All the action and plus the intention of that is what they intended to do, and that is how they reacted for eight years, I would be inclined to find that they had effectively withdrawn it and this comes under Section 4 and that they are exempt under Section 4 on this record as being a Class 4 job and with the expressed understanding that it is understood by all concerned that if there is the slightest doubt in the Food and Drug Act that [453] there is any harmful effects or any statutory reason why these drugs shouldn't be on the market they should seize them. If they seize them in this jurisdiction I can assure the government that they will get a full and fair hearing and determine whether or not it was a lawful seizure, and that is that. We will dispose of it accordingly.

I also am of the opinion since the Court has held that and at the urgency of the plaintiff, and I agree with him, that he is not what I will call a 3(b) party—of course, the ruling that the commission has made in reference to its Federal Register, you know, as far as I am concerned I am not passing on the validity of that ruling; it stands as far as I am concerned. He can do what he wants to if it is void. They can proceed to enforce it. He can neglect it. In other words, I am just not passing on it. I mean I am making it clear. In other words, the government is free to stand on their Federal Register support if they want to do it because he says he doesn't come within that section and I agree with him, and he's got to come within one, so he wants to come in the grandfather clause as an old drug, and I agree with him.

I will enter an order accordingly, and if either side wants it, they can't work this out, I will write more formal findings as soon as I can get to it. With my docket it may take me a week or two. If they want to accept, you know, my findings, just what oral ramblings that I have made, which [454] are not as definitive as it would be if I, you know, made specific findings and conclusions which I will.

I think I have clarified my situation.

Yes, sir?

Mr. HOFFMAN. Your Honor, may we submit proposed findings and conclusions?

The COURT. Yes, you may do that on this record, I say if you want more; and so can they. You can submit it to them, and the ones that they do not agree with the findings, I will do it accordingly. But so that you understand it they must be in accord with the general subject that I have just said here—

Mr. HOFFMAN. Very well.

The COURT (continuing). And that is to support that you are an old drug and that the old drug is based upon the fact that your application was always your intent to withdraw that and your affirmative acts effectively withdrew it before the effective date of this Act. I mean that is the basis of my putting you in the other category.

EXCERPTS FROM TRANSCRIPT OF PROCEEDINGS IN DISTRICT  
COURT ON MAY 4, 1971

[12] \* \* \*

Mr. HOFFMAN. Your Honor, the record showed that con-

struing the word "safe" to mean the illogical meaning that the court just described——

The COURT. So that we will get the record clear, I've got many things to do, and this isn't one of them—on page 4 you have asked me to confirm that I found No. 2 that were and are today generally recognized as safe for their intended uses as the word "safe" was then understood. I believe that I said that when I said that the court finds that these bioflavonoids were safe as that word was then understood.

Mr. HOFFMAN. That is fine.

The COURT. I don't know how I can say it any better.

[13] Mr. HOFFMAN. That is fine with us, your Honor.

The COURT. So whether you——

Mr. HOFFMAN. That disposes of No. 2.

The COURT. If that isn't what I said let them tell me what I said.

Mr. HOFFMAN. Fine, your Honor.

As to No. 1,——

The COURT. Now, as your No. 1, you asked me that they are exempt from the new-drug provisions of the statute.

Mr. HOFFMAN. That is correct, your Honor.

The COURT. Well, I couldn't have found that any better in your ways when I made it very clear that that is all I was doing.

Mr. HOFFMAN. That is right, your Honor.

The COURT. I held that this decision, the last paragraph is limited solely to the determination of whether the plaintiff's drugs are entitled to the exemption set forth in the statute; isn't that right? And I held that they were.

Mr. HOFFMAN. That is right, your Honor.

The COURT. Now, I limited it to the exemption.

Mr. HOFFMAN. The only thing we weren't clear on that, your Honor—well, we think we know what the court meant. Technically speaking, the exemption in Section 107(c)(4) is an exemption from the changes in the definition. Now, we are confident that the court intended to hold that the [14] products are exempt from new-drug regulation because of the consequences of their being exempt from the definition, and that was all we had in mind on our point 1 in which we asked the court to confirm that the products are today not new drugs under that old pre-1962 definition and, therefore, are exempt from the new-drug provisions of the statute.

If I understood the court a moment ago correctly, the court said, yes, that was what the court did hold, and that is the confirmation that we are seeking.

The COURT. The court clearly intended to hold that they were exempted by the grandfather clause. Now, that is all period.

Mr. HOFFMAN. Exempted by the grandfather clause from new-drug regulation.

The COURT. That is correct, and that is all I held.

They are not exempt—the government, if they think they are toxic, if the government thinks they are harmful, as I made it very clear in there—

Mr. HOFFMAN. We understand that, your Honor.

The COURT (continuing). The government can seize your drugs tomorrow and take them off the market—I mean under the pure Food and Drug Act. And I only held that they can't require you to go through all this rigmarole because the grandfather clause exempted them. \* \* \*

In the United States District Court for the Eastern District  
of Virginia

(Civil Action No. 4915-A)

USV PHARMACEUTICAL CORPORATION, PLAINTIFF

v.

ELLIOT L. RICHARDSON, ETC. ET AL., DEFENDANTS

#### ORDER AND MEMORANDUM OPINION

This Court is of the opinion that the plaintiff's bioflavonoids here in question are exempted from the provisions of §201(p) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, et seq., as amended by P.L. 87-781, so long as such products are intended solely for use under conditions prescribed, recommended or suggested in the labeling thereof, as of October 9, 1962, and

It Is So Ordered.

The controversy here turns on whether the plaintiff's bioflavonoids are "new drugs," within the meaning of 21 U.S.C. § 321(p), and thus subject to the efficacy review provisions of the amendment of 1902, or whether they are "old drugs" by reason of the "grandfather clause" in the 1962 amendment—§ 107(c)(4).

The Federal Drug Administration has determined that the plaintiff's bioflavonoids are "new drugs" and has called upon the manufacturer to document and establish their efficacy, as provided for in the 1962 amendment.



Rather than comply, or run the risk of criminal prosecution for non-compliance, the plaintiff brought this suit seeking pre-enforcement relief under 5 U.S.C. § 701-704 (Administrative Procedure Act) and 28 U.S.C. § 2201 (Declaratory Judgment Act). That such is proper to resolve conflicts of this type, see *Gardner v. Toilet Goods Association*, 387 U.S. 167 (1966).

The "grandfather clause," 107(c)(4) of the Act, reads as follows:

In the case of any drug which, on the day immediately preceding the enactment date [October 9, 1962], (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

If a statute grants exemptions to certain classes of products from its operation and a dispute arises as to whether or not a given product is entitled to such exemption, it is the Court's function—not the Administrator's—to determine whether or not such product is exempted. Thus, this Court has jurisdiction under the statutes above mentioned to hear and determine this controversy between the parties.

The Court's findings and conclusions follow.

The plaintiff has manufactured and sold its citrus line of bioflavonoid products in interstate commerce in substantial quantities from about 1955 to the present date.

Two of the plaintiff's products were never covered by effective new drug applications. The other seven were all covered at one time. These applications, however, were withdrawn prior to October of 1962. The plaintiff made that clear through its correspondence with the Federal Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDAs.—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by NDAs 11474 and 11475 were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid com-

pound in plaintiff's other products and that the recommended uses of all the CVP products are essentially the same.

From this evidence, the Court finds that none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962.

Whether the plaintiff's bioflavonoids are "new drugs" within the meaning of § 201(p) of the basic Act (codified as 21 U.S.C. § 321(p)) is the key question for determination here.

"The term 'new drug' means—

(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof. . . ."

The word "safe" as used in the basic Act refers to the health of man or animal<sup>1</sup>—efficacy was not added until the 1962 amendment.

Measured by the standard employed by the Federal Drug Administration prior to the effective date of the 1962 amendment, the Court finds that the plaintiff's bioflavonoids were "safe," as that word was then understood.

All of the expert witnesses, including those called by the Government, were of the opinion that the plaintiff's bioflavonoids were innocuous when taken by anyone in any condition.

All agreed they were non-toxic and harmless per se, in that a normal individual given such a product would not develop an adverse reaction, and were safe for use under the conditions prescribed, recommended or suggested in the labeling—that is, abnormal capillary permeability and fragility—The plaintiff's experts went further—They said the plaintiff's bioflavonoids were not only safe but were quite effective, when used as recommended, in certain types of capillary bleeding.

The Government's experts contend that the safety of a drug can only be determined by its efficacy—a "safe drug" becomes "unsafe" when used in place of the proper drug—the harm comes from the failure to use the best known drug for the treatment of the ailment complained of. This may or may not be so under the 1962 amendment—the Court does not determine that question here.

This decision is limited solely to the determination of whether

<sup>1</sup> 21 U.S.C. § 321(u).



the plaintiff's drugs are entitled to the exemption set forth in § 107(c)(4) of the Act.

The Clerk will send a copy of this order and memorandum opinion to all counsel of record.

(S) OREN R. LEWIS,  
*United States District Judge.*

April 1, 1971

In the United States Court of Appeals for the Fourth Circuit

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee*,

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, WELFARE, AND HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, *Appellants*.

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria. Oren R. Lewis, District Judge.

(Argued December 8, 1971.

Decided May 24, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges

Howard S. Epstein, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, Bruce B. Wilson, C. Coleman Bird, and Cheryl S. Karner, Attorneys, Department of Justice, and Peter Barton Hutt, Assistant General Counsel, Joanne S. Sisk, Richard S. Silverman, Attorneys, Food, Drugs, and Environmental Health Division, Department of Health, Education, and Welfare, on brief) for Appellants, and Joel Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader, Nicholson and Ross on brief) for Appellee.

RUSSELL, Circuit Judge:

Unlike the drug manufacturers in *Bentex*,<sup>1</sup> this plaintiff markets a line of citrus bioflavonoid drugs,<sup>2</sup> of which all but

<sup>1</sup> *Bentex Pharmaceuticals, Inc. v. Richardson*, No. 71-1243 (4th Cir., appeal docketed March 11, 1971).

<sup>2</sup> "Bioflavonoid" is defined in Dorland's Illustrated Medical Dictionary, 2d Edition, as follows: "a generic term for a group of compounds which are

two were covered by NDAs issued at various times in 1955 and 1956. Like the plaintiffs in *Bentex*, however, it seeks by an action for declaratory judgment to secure the benefit of the exemption available under the "grandfather clause"<sup>3</sup> from the enlarged definition of a "new drug" included in the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The defendants, who are the Secretary of Health, Education and Welfare (hereinafter referred to as HEW) and the Commissioner of the Food and Drug Administration (hereafter referred to as Commissioner), urge that jurisdiction should be refused on two grounds: 1. Primary jurisdiction lies with HEW; and 2. Failure to exhaust administrative remedies. They, also, attack the right of the plaintiff to claim the exemption. The District Court sustained jurisdiction and, largely on the basis of a Stipulation of Facts, upheld plaintiff's right to the statutory exemption both for its NDA'd and its non-NDA'd drugs. We reverse.

The threshold question raised by the defendants and overruled by the District Court may be quickly disposed of. Under similar circumstances in *Bentex*, we sustained the right of the District Court to entertain an action for declaratory judgment. We reach the same result here. Since we dismiss the claim of the plaintiff for exemption on behalf of its drugs on substantive grounds, it is unnecessary to consider the additional objection that plaintiff has failed to exhaust administrative remedies.

The substantive issue posed by this action is the right of the plaintiff to the exemption provided by Section 107(c)(4) from the revised definition of "new drug" incorporated in the 1962 Amendments. In resolving that issue, we must differentiate, even as the "grandfather clause" itself does, between the plaintiff's drugs, which were covered by an "effective NDA",<sup>4</sup> and those, which were marketed without an NDA. The Act makes a distinction in "grandfather" rights between a drug marketed under an NDA<sup>5</sup> and one marketed without an NDA. In the case

widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels." Stipulation of Facts, #4.

<sup>3</sup> Section 107(c)(4), Pub. L. 87-781 (1962), 21 U.S.C., 1972 Supplement, pp. 191-2.

<sup>4</sup> "Effective", as used in this phrase, means simply approved. Hagan. *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm., L. J., 119, p. 121.

<sup>5</sup> This is the term used to describe an approved preclearance application under Section 355.

of a drug covered by a previously approved NDA, the 1962 Amendments required the Secretary to withdraw the approved NDAs if after notice and opportunity of hearing, the applicant failed to file substantial evidence<sup>6</sup> that the drug previously approved is both safe and effective.<sup>7</sup> For such drugs, however, a grace period or temporary "grandfather right" was granted. Under it, the manufacturer was given two years within which to develop his showing of effectiveness and, during this period, the Secretary was prohibited from withdrawing or suspending the previously granted NDA.<sup>8</sup> On the other hand, a non-NDA'd drug which met the criteria stated in Section 107(c)(4) was exempted permanently from the amended definition of "new drug" made by the 1962 Amendments and was thereby relieved of securing an approved NDA as a condition for marketing clearance. The statutory criteria for this permanent "grandfather" exemption are stated as "any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined in Section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under Section 505 of that Act".

It is the contention of the plaintiff that all its drugs in question, both those previously NDA'd and those not, are protected by the permanent "grandfather clause" (i.e., Section 107(c)(4)). Because the statute seemingly makes a distinction between the two, it is proper to consider separately the two groups of drugs: i.e., those having NDAs and those without NDAs.

Taking up first plaintiff's NDA'd drugs: There is no dispute that such drugs met criteria (A) and (B), as set forth in the "grandfather clause", but the defendants seriously dispute the claim that they meet condition (C). Facially at least, this contention of the defendants seems unanswerable. These drugs are "covered by an effective application" or NDA, and are thus specifically barred by condition (C) from qualifying for exemption from the application of the effectiveness Amendments of 1962. The District Court found, however, that before "the day immediately preceding the enactment date", which was October 9, 1962, the previously granted NDAs had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA on the crucial date of Octo-

<sup>6</sup> "Substantial evidence" is defined in the Act (21 U.S.C. 355(d)).

<sup>7</sup> Section 355(e), 21 U.S.C.

<sup>8</sup> Section 107(c)(3)(B), 21 U.S.C., note foll. Section 321.

ber 9, 1962. The error in this reasoning, however, is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. While an applicant may, during the pendency of his application, withdraw his application, he has no such right after approval of the application by the Secretary. At that point only the Secretary can withdraw the approval. As one commentator has accurately summed up, "It is true that a manufacturer may withdraw a pending NDA. Sec. 21.C.F.R. sec. 130.8 (1971). However, no provision in the law permits a manufacturer to withdraw an effective NDA; only FDA can do so through Section 505(e) procedure".\* Prior to October 9, 1962, there was in this case no proceeding by FDA under Section 505(e) with reference to plaintiff's NDA'd drugs and there was accordingly no valid withdrawal of the plaintiff's effective NDAs, on or before the enactment date of the 1962 Amendments.

The plaintiff, though, presses another theory upon the basis of which it claims the previously issued NDAs are to be regarded as ineffective on October 9, 1962. Thus it argues that its pre-1962 NDA'd drugs became generally recognized as safe on or before October 9, 1962. So much the defendants seem to concede in the Stipulation of Facts submitted to the District Court. From this fact, it reasons that its NDA drugs ceased to be "new drugs" as defined in the Act, on or before October 9, 1962, and, ergo, its previously issued NDAs were no longer needed or "effective" on the critical date of October 9.<sup>10</sup> The difficulty with this argument, plausible though it may be, is that it would make surplusage of requirement (C) in the exemption statute. Thus, if a drug met the test set up in (B), that is, was generally recognized as safe on October 9, 1962, it would not be necessary, under the plaintiff's argument, to consider whether (C) was applicable or not. Such a construction of the exemption statute, under which a clearly stated condition to its application is to be treated as a nullity, offends the well-settled rule of statutory construction that all parts of a statute are to be given effect if at all possible.<sup>11</sup> It is manifestly

\* Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185 at p. 198, n. 77 (1971).

<sup>10</sup> See Barth, *Following the NAS-NRC Effectiveness Review, What?*, 22 Business Lawyer, 1185, 1187 (1967).

<sup>11</sup> *Jarecki v. G. D. Scarle & Co.* (1961) 367 U.S. 303, 307; *Ginsberg & Sons v. Popkin* (1932) 285 U.S. 204, 208.

possible to give effect to the conditions enunciated in both (B) and (C). There are many drugs that satisfy both conditions, that is, are generally recognized as safe and effective and are being marketed without an approved NDA. There is nothing inconsistent in the two requirements. Moreover, condition (C) represented a limitation on the right to an exemption that the Congress clearly and unmistakably intended to apply. The Congress never intended that a drug being marketed under an approved NDA might qualify under the "grandfather clause." This is plain from the comment in the Conference Committee Report that the exemption was to apply "to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure*". (Italics added.) H.R. Rep. 2526, 87th Cong., 2d Sess., p. 23. Moreover, the argument of the plaintiff would run counter to the principle that statutory exemptions, particularly as applied to statutes concerned with public health and safety, are to be strictly and narrowly construed.<sup>12</sup>

The plaintiff has, however, two drugs,<sup>13</sup> involved in this proceeding, which were generally recognized as safe and were<sup>14</sup> marketed as "old drugs" without an approved NDA on October 9, 1962. These drugs, as we earlier indicated, present separate problems from those drugs for which there are approved NDAs. They fall into the category of what are generally described in the trade as "me-too" drugs.<sup>15</sup> Such a drug, if generally regarded as safe on October 9, 1962, meets literally the criteria for exemption stated in the "grandfather clause". To sustain the exemption, however, creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege absent substantial evidence of effectiveness, whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4). Most commentators, while admitting the incongruity of this result, justify it as one compelled by the literal

<sup>12</sup> *United States v. Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. denied 385 U.S. 899.

<sup>13</sup> Duo-C.V.P. with Vitamin K Capsules and Bivam.

<sup>14</sup> Stipulation of Facts, Number 17.

<sup>15</sup> A "me-too" drug is generally defined as "one which is equivalent to another, pioneer drug, which preceded it on the market." Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 198, n. 78 (1971).

language of the statute.<sup>16</sup> Their reasoning is similar to that of the Court in *Pfizer, Inc. v. Richardson* (2d Cir. 1970) 434 F. 2d 536, 542, where speaking to a somewhat illogical provision in this same Act, Judge Friendly said: "A sufficient answer is the simple if not altogether satisfying one that Congress said so"<sup>17</sup> The FDA itself has recognized the vexing problem presented by the "me-too" drug and has sought to resolve it by a change in its position on the scope and application of an NDA.

It is the contention of the FDA that an approved NDA covers not merely the marketing of the parent but also its "me-too" offsprings and for that reason the "me-too" drugs have been permitted to be marketed without an NDA. Accordingly, under this theory, the withdrawal of the approved NDA of the pioneer operates as a withdrawal of marketing rights for the "me-too", unless the latter, either individually or in conjunction with its pioneer, provides substantial evidence of effectiveness. This view has, however, been severely criticized and with considerable reason. It is, as one critic has observed, "at variance with the uniform position it (FDA) has taken over the years with regard to the nature of NDAs." This position, which is termed the "personal approach" holds that "Section 505 applies to drugs as individual articles, not as collective groups, and that each manufacturer of a new drug must file his own NDA." This critic concludes with the observation that it is "an unjustifiable exercise in semantics to say that a drug legally marketed without an NDA was 'covered' by the NDA of another manufacturer's drug."<sup>18</sup>

That the policy of FDA has heretofore been contrary to the position now taken by it is further illustrated by the circum-

<sup>16</sup> See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203 (1971):

Surely, me-too drugs never processed through the new procedures satisfy all the requirements of section 107(c) (4).

To the same effect is Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L.J., 119, at pp. 125-6. D'Andrade, *The Effect of NAS-NRC Review on Me-Too and Post-62 Drugs*, 25 Food, Drug, Cosm. L.J., 330, 334 (1970).

<sup>17</sup> This, of course, is not the only inequity in the Amendments. There are other inequities, as FDA freely conceded at a House Hearing before a Subcommittee of the Commission on Government Operations on Drug Efficacy, Part 2, 91st Cong., 1st Sess. (1969), pp. 384-5.

<sup>18</sup> Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203, n. 111 (1971).

stances under which at least one of the "me-toos" of the plaintiff began marketing. Prior to marketing Bivam, one of its "me-toos" similar in formula to other drugs previously NDA'd by it, the plaintiff inquired of FDA whether it was an "old drug" entitled to be marketed without an NDA. FDA, after reviewing its composition and labeling, advised the plaintiff it was a product "generally regarded as safe" (and thus an "old drug") and could be marketed without an NDA. There was no suggestion by the plaintiff that it sought to market this drug under any previous NDA granted one of its products nor did the FDA base its advice on that basis. Both the plaintiff and FDA assumed at that time that a "me-too" drug, which had become generally recognized as safe, was entitled to be marketed without an NDA; in short, that the qualification for marketing a "me-too" drug was general recognition of safety and not the NDA of its pioneer.

It would seem that the consistent construction of the Act by the FDA for thirty years<sup>19</sup> and a construction which accords with the literal language of the Act itself may only be changed by Congress itself.<sup>20</sup> In fact, the General Counsel of FDA, in testimony before a House Subcommittee Hearing on Drug Efficacy, Part 2 (91st Cong., 1st Sess., 1969) p. 375, expressed the wish that Congress would "pass" a clarifying amendment on this issue, conceding that the position of his agency was in considerable doubt.

<sup>19</sup> See, Hagan, *supra*, at p. 125:

Furthermore, the concept that new drug clearance by one manufacturer affects the rights of subsequent manufacturers is inconsistent with the established doctrine that new drug clearance is *personal* to the applicant, and does not embrace the drug *per se*.

<sup>20</sup> Cf., comment in Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal 185, at pp. 206-7 (1971):

Ultimately the issue of the status of me-too drugs will have to be squarely faced, and the FDA interpretation of section 107(c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts. In that event the agency will undoubtedly ask Congress for new legislation to remedy the situation. In view of the obvious inequities in the present situation, this would seem to be the most desirable solution.



But even if it be assumed that "me-too" drugs are generally entitled to Section 107(c)(4) protection, provided they were generally recognized as safe on October 9, 1962, that does not resolve the right of the plaintiff's "me-toos" to exemption. As has been pointed out, the reasoning on which "me-toos" are regarded as not covered by the NDAs granted the manufacturers of their pioneers is that an NDA is regarded as "personal" to the manufacturer submitting the application and to the drug covered. But in this case, the "me-toos" are similar in formula and labeling to other drugs for which the plaintiff itself applied and obtained NDAs. It is true that, in the case of one drug at least, to which reference has already been made, plaintiff's "me-toos" were regarded as exempt, not because plaintiff had an approved NDA for a similar drug, but because FDA was of the opinion that it met the requirements for classification as an old drug. Nonetheless, it is the "personal" character of the NDA that has been deemed as the basis on which it is contended that the "me-toos" are not covered by the NDA granted another manufacturer, albeit the drugs involved may be similar. That reasoning manifestly cannot sustain a right of exemption in favor of plaintiff's "me-toos". The plaintiff's NDAs, being "personal" to it, would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula, between plaintiff's NDA'd drugs and its "me-toos" is stipulated. Under those circumstances, both the NDA'd and the "me-too" drugs will be treated alike and neither can qualify for exemption under the terms of Section 107(c)(4). It is recognized that this conclusion places the plaintiff in a less favorable position than that occupied by others who may have copied its product prior to October 9, 1962. That inequity is, however, inherent in the law and may only be redressed by Congress, not by the Courts under the guise of construction.

Reversed, with directions to enter judgment for the defendants.

REVERSED.



[Filed May 24, 1973]

JUDGMENT

IN THE UNITED STATES COURT OF APPEALS FOR THE  
FOURTH CIRCUIT

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No. 71-1596

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USV PHARMACEUTICAL CORPORATION, APPELLEE,

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION,  
AND WELFARE, DEPARTMENT OF HEALTH, EDUCATION, AND  
WELFARE, AND HERBERT L. LEY, JR., COMMISSIONER OF FOOD  
AND DRUGS, FOOD AND DRUG ADMINISTRATION, APPELLANTS.

*Appeal from the United States District Court for the Eastern  
District of Virginia*

This cause came on to be heard on the record from the United States District Court for the Eastern District of Virginia, and was argued by counsel.

ON CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this case, be, and the same is hereby, reversed.

SAMUEL W. PHILLIPS, Clerk.

In the Supreme Court of the United States

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER,

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION  
AND WELFARE, ET AL.

ORDER ALLOWING CERTIORARI. Filed January 8, 1973.

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72-394, 72-414, 72-528 and 72-555, and a total of three hours is allotted for oral argument.

# RELEVANT STATUTES AND REGULATIONS

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*:

SEC. 201 [321]. For the purposes of this Act—

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

SEC. 301 [331]. The following acts and the causing thereof are hereby prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 404 or 505.

SEC. 302 [332]. (a) The district courts of the United States and the United States courts of the Territories shall have juris-

Note—References in brackets [ ] are to title 21 U.S. Code.

diction, for cause shown, and subject to the provisions of section 381 (relating to notice to opposite party) of Title 28, to restrain violations of section 301 of this title, except paragraphs (h), (i), and (j) of said section.

SEC. 303 [333]. (a) Any person who violates a provision of section 301 shall be imprisoned for not more than one year or fined not more than \$1,000, or both.

SEC. 304 [334]. (a) (1) Any article of food, drug, device, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not, under the provisions of section 404 or 505, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which the article is found: *Provided, however,* That no libel for condemnation shall be instituted under this Act, for any alleged misbranding if there is pending in any court a libel for condemnation proceeding under this Act based upon the same alleged misbranding, and not more than one such proceeding shall be instituted if no such proceeding is so pending, except that such limitations shall not apply (A) when such misbranding has been the basis of a prior judgment in favor of the United States, in a criminal, injunction, or libel for condemnation proceeding under this Act, or (B) when the Secretary has probable cause to believe from facts found, without hearing, by him or any officer or employee of the Department that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the purchaser or consumer. In any case where the number of libel for condemnation proceedings is limited as above provided the proceeding pending or instituted shall, on application on the claimant, seasonably made, be removed for trial to any district agreed upon by stipulation between the parties, or, in case of failure to so stipulate within a reasonable time, the claimant may apply to the court of the district in which the seizure has been made, and such court (after giving

the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business to which the case shall be removed for trial.

(2) The following shall be liable to be proceeded against at any time on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which they are found: (A) Any drug that is a counterfeit drug, (B) Any container of a counterfeit drug, and (C) Any punch, die, plate, stone, labeling, container, or other thing used or designed for use in making a counterfeit drug or drugs.

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by

written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness

of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is presented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access

to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

\* \* \* \*

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for



leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

\*     \*     \*     \*     \*

SECTION 107 (C) OF PUBLIC LAW 87-781, 76 STAT. 788-789,  
NOTE FOLLOWING 21 U.S.C. 321 (1970 ED.):

SEC. 107(c)(1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act insofar as such amendments relate to the effectiveness of drugs shall not, so long as approval of such



application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the first day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, 52 STAT. 1040, PRIOR TO THE HARRIS-KEFAUVER AMENDMENT OF 1962 (21 U.S.C. 301 ET SEQ. (1958 ED.)):

SEC. 201[321]. For the purposes of this chapter—

(p) The term "new drug" means—

(1) Any drug the composition of which is such that such

drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to former sections 1-5 and 7-15 of this title, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

\* \* \* \* \*

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) (1) An application provided for in subsection (b) of this section shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date of the application to such time (not more than one hundred and eighty days after the filing thereof) as the Secretary deems necessary to enable him to study and investigate the application.

(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions, he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.

(e) The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds (1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective, or (2) that the application contains any untrue statement of a material fact. The order shall state the findings upon which it is based.

THE ADMINISTRATIVE PROCEDURE ACT, 80 STAT. 381 (5 U.S.C. 551

ET SEQ.)

#### § 554. Adjudications.

(a) This section applies, according to the provisions thereof, in every case of adjudication required by statute to be determined on the record after opportunity for an agency hearing, except to the extent that there is involved—

(1) a matter subject to a subsequent trial of the law and the facts de novo in a court;

(2) the selection or tenure of an employee, except a hearing examiner appointed under section 3105 of this title;

(3) proceedings in which decisions rest solely on inspections, tests, or elections;

(4) the conduct of military or foreign affairs functions;

(5) cases in which an agency is acting as an agent for a court; or

(6) the certification of worker representatives.

(b) Persons entitled to notice of an agency hearing shall be timely informed of—

(1) the time, place, and nature of the hearings.

(2) the legal authority and jurisdiction under which the hearing is to be held; and

(3) the matters of fact and law asserted.

When private persons are the moving parties, other parties to the proceeding shall give prompt notice of issues controverted in fact or law; and in other instances agencies may by rule require responsive pleading. In fixing the time and place for hearings, due regard shall be had for the convenience and necessity of the parties or their representatives.

(c) The agency shall give all interested parties opportunity for—

(1) the submission and consideration of facts, arguments, offers of settlement, or proposals of adjustment when time, the nature of the proceeding, and the public interest permit; and

(2) to the extent that the parties are unable so to determine a controversy by consent, hearing and decision on notice and in accordance with sections 556 and 557 of this title.

(d) The employee who presides at the reception of evidence pursuant to section 556 of this title shall make the recommended decision or initial decision required by section 557 of this title, unless he becomes unavailable to the agency. Except to the extent required for the disposition of ex parte matters as authorized by law, such an employee may not—

(1) consult a person or party on a fact in issue, unless on notice and opportunity for all parties to participate; or

(2) be responsible to or subject to the supervision or direction of an employee or agent engaged in the perform-

ance of investigative or prosecuting functions for an agency.

An employee or agent engaged in the performance of investigative or prosecuting functions for an agency in a case may not, in that or a factually related case, participate or advise in the decision, recommended decision, or agency review pursuant to section 557 of this title, except as witness or counsel in public proceedings. This subsection does not apply—

(A) in determining applications for initial licenses;

(B) to proceedings involving the validity or application of rates, facilities, or practices of public utilities or carriers; or

(C) to the agency or a member or members of the body comprising the agency.

(e) The agency, with like effect as in the case of other orders, and in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty.

#### § 702. Right of review.

A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof.

#### § 703. Form and venue of proceeding.

The form of proceeding for judicial review is the special statutory review proceeding relevant to the subject matter in a court specified by statute or, in the absence or inadequacy thereof, any applicable form of legal action, including actions for declaratory judgments or writs of prohibitory or mandatory injunction or habeas corpus, in a court of competent jurisdiction. Except to the extent that prior, adequate, and exclusive opportunity for judicial review is provided by law, agency action is subject to judicial review in civil or criminal proceedings for judicial enforcement.

#### § 704. Actions reviewable.

Agency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review. A preliminary, procedural, or intermediate agency action or ruling not directly reviewable is subject to review on the review of the final agency action. Except as otherwise expressly required by statute, agency action otherwise final is final for the purposes of this section whether

or not there has been presented or determined an application for a declaratory order, for any form of reconsiderations, or, unless the agency otherwise requires by rule and provides that the action meanwhile is inoperative, for an appeal to superior agency authority.

21 C.F.R. 130.12(a) (5) as amended, 35 F.R. 7251, May 8, 1970, provides:

(a) If the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to the new drug, that \* \* \*

(5)(i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of suscepti-

bility and exposure to the condition against which prophylaxis is desired.

(ii) Assigns the subjects to test groups in such a way as to minimize bias.

(iii) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(iii) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(iv) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in



certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis, and and evaluation of data derived from the study, including any appropriate statistical methods.

*Provided, however,* That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding non-conformance with the criteria for which waiver is requested.

(b) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(c) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the



approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(6) Based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; the Commissioner shall within 180 days after the filing of the application inform the applicant in writing of his intention to issue a notice of hearing on a proposal to refuse to approve the application.

(b) Unless by the 30th day following the date of issuance of the letter informing the applicant of the intention to issue a notice of hearing, the applicant,

(1) Withdraws the application; or

(2) Waives the opportunity for a hearing; or

(3) Agrees with the Commissioner on an additional period to precede issuance of such notice of hearing,

the Commissioner shall expeditiously notify the applicant of an opportunity for a hearing on the question of whether such application is approvable as provided in § 130.14.

21 C.F.R. 130.14, as amended, 35 F.R. 7252, May 8, 1970, provides:

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue an order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the Federal Register and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hear-

ing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(c) The hearing will be open to the public: *Provided, however,* That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.